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Editorial

Circle of Willis. Functional Concepts, Old and New

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In 1664, Thomas Willis described the arterial circle at the base of the brain and developed certain concepts concerning function which have undergone little real change. The purpose of this discussion is to re-evaluate certain functional concepts of the circle of Willis as they are routinely considered and presented to the medical student in his beginning years of study. Unfortunately, the old and tried concepts often acquire a certain dignity through repetition and are passed down unmodified through the years.

The circle of Willis is conceived by many as serving to retard the flow of blood, and through its angles, branches, and cross-communicating channels insuring uninterrupted circulation to the brain at regulated pressures. The acute angulations of the internal carotid artery and the vertebral arteries as they enter the cranium often have been construed as a mechanical safeguard against excessive intracerebral pressure; the communicating channels are generally viewed to function as provisions for collateral circulation in case of partial or complete occlusion of the main sources of supply. These functional concepts might seem more logical if the components of the circle of Willis were bilaterally symmetrical, both in arrangement and diameters. That this situation does not exist in man has been demonstrated through extensive anatomic studies, especially those accumulated during recent years.

Earlier concepts of the characteristics of blood flow through these cross-communicating channels have been revised. Prior to the injection studies of Kramer,[3] the prime function of the circle of Willis was said to be that of mixing the blood passed to its primary branches. His studies indicate that mixing between right and left sides is minimal. More recently, MacDonald and Potter[4] established

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that flow through the circle of Willis is laminar, thus providing for optimal flow with respect to pressure. These authors consider the basilar artery as an efficient anastomosis between the vertebral sources of supply, providing for adequate circulation to the vital centers of the brain stem and serving as a protective mechanism in partial occlusion of the vertebral arteries. Heretofore, the basilar artery never has been considered as an efficient anastomotic channel between the right and left sources of supply. A similar function may be assigned to the anterior communicating artery. Through descriptions of the circle of Willis in modern texts, one obtains the impression that the anastomosis of prime functional importance is formed by the posterior communicating arteries. It is emphasized that by virtue of position, these connections serve for adequate cross flow between internal carotid and vertebral sources of supply. That this arrangement cannot be so construed functionally is supported by developmental concepts which are to be presented.

Many variations of the anatomic components of the circle have been described. Excluding primary structural abnormalities, such as aneurysms, the variants frequently encountered in the adult arise from developmental defects of the anterior and posterior communicating arteries. These variant patterns reflect preferential channeling of blood as the embryonic pattern of the circle of Willis is modified during development. Three primary variants of the circle are described. In the primitive pattern, the posterior cerebral arteries originate from the internal carotid artery. When present in the adult, this represents a developmental arrest in which anastomotic connections between posterior divisions of the internal carotid and and the basilar artery have been established but have remained diminutive in size. In the transitional arrangement of vessels, the posterior communicating arteries and posterior cerebral arteries are equal in diameter. In the "normal" adult configuration the posterior communicating arteries are attenuated, the posterior cerebral vessels arising as terminal branches of the basilar artery. Thus, in the normal adult configuration, the posterior cerebral arteries are in part derived from the internal carotid artery and in part represent a new vascular connection between the internal carotid and the basilar artery. Differentiation of the circle thus progresses toward virtual obliteration of the posterior communicating arteries as functional anastomoses. If equal distribution of blood and equalization of pressure were prime functions of the circle of Willis, symmetry of arrangement and uniformity in caliber of component parts might be expected. If anastomotic protection is important, it is surprising that the posterior communicating arteries would become attentuated, or even obliterated, as development progresses.

Three hundred circles of Willis studied by Kirgis and associates[2] were examined for variations in anatomic pattern which might explain the clinical variation in response to occlusion of one common carotid artery in patients of similar cardiovascular status. These authors describe three common variations which represent modifications in the contribution of the internal carotid artery to the circle of Willis which would alter the field of carotid arterial supply to the cerebrum. Significant variations from the textbook pattern regarding arrangement and diameter of components was present in over 50 per cent of the circles

studied. These findings seem to be inconsistent with functional concepts which depend upon the assumption of equal distribution of cerebral blood.

Injection experiments, in which normal pressure gradients were maintained in the living animal, have shown that dye injected into one vertebral artery fills both posterior communicating arteries to a point about at the mid-lengths. Similarly, dye injected into one internal carotid artery fills the middle and anterior cerebral arteries of that side; only half the length of the anterior communicating artery is filled. In the normal circle, these nodal points of stasis are not fixed, but tend to shift position with normal variations in pressure gradients between arteries. The typical adult posterior communicating artery is so slender that little collateral circulation is to be expected of it should blood flow be critically reduced at the vertebral-basilar level. Integrity of the vertebral circulation is, therefore, of prime importance for the maintenance of the brain stem, cerebellum, and that part of the cerebrum supplied by the posterior cerebral artery. In this connection, an important source of collateral blood supply between the posterior and middle cerebral arteries has been neglected. This anastomosis exists in the region of the lateral geniculate body between the anterior and posterior choroidal arteries; these vessels are larger when the posterior communicating artery is attenuated. The anterior and posterior choroidal arteries have been virtually neglected as channels providing for cross communication between the vertebral and carotid circulations. These vessels are not even considered to be prime components of the arterial circle, although their size and fields of distribution establish them as important anastomotic channels anatomically.

So far, our consideration has only involved the various anatomic components of the circle of Willis. The question of laminar flow and turbulence has been mentioned, but functional concepts of the circle of Willis contain little that has to do with relationship between turbulence and laminar flow, as they may be modified by atheromata, tortuosity, reduced diameters of vessels, and other changes. Turbulence induced by atheromata produces little change in the laminar flow properties of the circulation in a large vessel, such as the aorta, or in its primary branches where flow velocity and diameters are large. For a 1,400-Gm. brain, the vertebral-basilar arterial supply approaches 300 c.c. per minute. Since diameters here are small, atheromata and tortuosity may produce significant degrees of turbulence with increased frictional resistance and reduced blood flow. It is conceivable that the reduction in blood flow may actually approach critical levels, especially where the small branches arise at nearly right angles to the parent vessel. Dickinson and Thompson[1] have published data correlating the postmortem flow rates through the vertebral arteries with the mean brachial arterial pressure during life. The coefficients of the correlation were highly significant ($r = 0.763$; $P = 1 \times 10^{-9}$). This correlation has an increased significance when it is emphasized that the adult circle of Willis is not an efficient anastomotic ring, is not bilaterally symmetrical, and does not efficiently distribute blood between the carotid and vertebral circulations; thus, the sources of supply in those segments of the brain stem which contain vasomotor centers are virtually confined to the vertebral arteries. These authors suggest that the rise in mean blood pressure seen in the aged or in younger persons with essential hypertension

may represent a reflex vasomotor phenomenon assuring adequacy of their vertebral circulation in the presence of an increased resistance brought about by the development of turbulence.

That the circle of Willis functions as a simple anastomotic ring seems to be an oversimplification of the facts. The system of intercommunicating channels is too variant in structural characteristics to support any single functional concept, and it seems that more precise studies are necessary to clarify the various factors involved in the regulation of cerebral circulation by the circle of Willis. The anatomic variations involved in the circle of Willis must be defined precisely as regards (1) symmetry of the circle, (2) diameters of component vessels in the circle, (3) alterations in elasticity of vessel walls, and (4) the association or correlation between sites of intracerebral hemorrhage, encephalomacia, and atheromatous changes in the wall of the blood vessels.

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Clinical Communications

Arteriovenous Fistula: Hemodynamic Effects of Occlusion and Exercise

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The adjustment of cardiac output for the maintenance of tissue metabolic requirements may be accomplished through several mechanisms. In thyrotoxicosis and anemia, this end is apparently achieved by both an increased stroke volume and heart rate,[1] in contrast to the usual manner in which the exercising normal human being attempts to handle greater requirements for oxygen, that is, by increasing heart rate.[2,3] Moreover, the exercise response in these states of high cardiac output is met largely by increments of stroke volume.[1] The special situation of systemic chronic arteriovenous fistula, in which significant blood is diverted from tissue-perfusing capillaries, may also maintain effective blood flow largely in the same manner. Evaluation of the conventional exercise response in these patients is complicated, however, by the effects of skeletal muscle contraction upon the fistula itself when located in the leg. These considerations form the background of this hemodynamic study in 7 patients with chronic peripheral arteriovenous fistula.

MATERIALS AND METHODS

The patient material consisted of 7 individuals, ranging in age from 16 to 63 years, who had typical symptoms and signs of peripheral arteriovenous fistula. The important clinical and laboratory findings in these patients are given in Table I. All cases were the result of gunshot injuries. The traumatic fistulas were located in the lower extremity in 6 patients and in the upper extremity in 1 patient. One patient (P. A.) was in congestive heart failure, whereas the other 6 patients had no symptoms or signs of heart failure at the time of study. The heart size varied between 0 and +87 per cent of the predicted size, with an average of +32 per cent, using the criteria of Ungerleider.[4] Anemia was not present in any of the patients.

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Right heart catheterization was carried out with the patient in the fasting state. To decrease apprehension, each patient was given 100 mg. of Nembutal one-half hour before the procedure was initiated. A double-lumen catheter was employed; the distal opening was wedged in a branch of the pulmonary artery in order to obtain pulmonary "capillary" pressures, and the proximal lumen was in the pulmonary artery. An indwelling Cournand needle was placed in the brachial artery in order to obtain arterial pressures and blood samples. With the patients in the resting state and the fistula open, cardiac outputs were determined by the Fick principle.[5] Immediately after the determination of cardiac output, simultaneous pulmonary "capillary," pulmonary arterial, and brachial arterial pressures were recorded. The fistula was then occluded by applying a blood-pressure pneumatic cuff proximal to the fistula and inflating it to a pressure slightly above the arterial systolic blood pressure. Repeat determinations of cardiac output and pressures were made 5 minutes after the occlusion was applied. With the fistula open, all of the patients were then exercised on a bicycle ergometer at approximately the same load for 5 minutes. Simultaneous pressures from the pulmonary "capillary," pulmonary artery, and brachial artery were recorded each minute during the period of exercise. Expired air for the determination of oxygen consumption was collected between 3 and 4 minutes, and blood was drawn simultaneously from the brachial and pulmonary arteries over the entire period of air collection. In 5 patients, similar exercise studies were repeated with the fistula occluded. Blood samples were analyzed for content of oxygen by the method of Van Slyke and Neill.[6] Oxygen in the expired and inspired air was measured by means of a Pauling oxygen analyzer; a correction factor of 1.007 converted the expired volume to the inspired volume.[3] Peripheral and pulmonary arteriolar resistances were calculated according to accepted formulas.[7]

TABLE I. CLINICAL AND LABORATORY DATA

NAME, SEX, AGE	CAUSE	LOCATION OF FISTULA	DURATION OF FISTULA	CARDIAC ENLARGEMENT (PER CENT ABOVE PREDICTED NORMAL*)	HEMOGLOBIN (GM./100 C.C.)
M.R. Female 44	Gunshot	Right calf Popliteal fossa	20 yr.	79	14.6
E.H. Male 31	Gunshot	Right popliteal	12 yr.	49	11.9
T. S. Male 45	Gunshot	Right calf	25 yr.	3	13.5
I.T. Male 49	Gunshot	Left thigh	35 yr.	39	12.4
H.J. Male 31	Gunshot	Left shoulder	4 yr.	43	14.6
P.A.† Male 63	Gunshot	Popliteal fossa	48 yr.	56	14.6
W.R. Male 16	Gunshot	Right calf	1 mo.	23	12.4

*According to Ungerleider.
†Hypertensive.

RESULTS

The hemodynamic data are presented in Table II. With the patient in a state of rest, and with the fistula open, the cardiac index was high in all patients except one (P.A.), with a range from 3.7 to 23.9 L./min./M.²BSA. The average for the group was 7.9 L./min./M.²BSA, as compared with normal values in this laboratory of 3.55 ± 0.17 L./min./M.²BSA. The cardiac index of 23.9 L./min./M.²BSA obtained in Patient E. H. is the largest reported in a patient with arteriovenous fistula. Upon occlusion of the fistula with the patient in the resting state, the average cardiac index decreased from a control value of 7.9 to 3.9 L./min./M.²BSA. During exercise without occlusion, although the expected increase in cardiac index occurred in 3 patients, substantial decline was observed in 3 instances. The patient (P.A.) who was in heart failure showed a slight increase in cardiac index. Exercise was repeated in 5 subjects after occlusion of the fistula. The response of cardiac output to exercise under these circumstances was uniformly lower than when the fistula was open.

Consumption of oxygen at rest was slightly increased; it averaged 148 c.c./min./M.²BSA, with a range of 120 to 182 c.c./min./M.²BSA, as compared to our normal values of 139 ± 6.8 c.c./min./M.²BSA. Occlusion of the fistula caused a decrease in the consumption of oxygen in 3 patients and an increase in 3 patients. During a constant state of exercise, with the fistula open, the consumption of oxygen increased in all patients; the increment above the resting level ranged from 63 to 520 c.c./min./M.²BSA, with an average increment of 231 c.c./min./M.²BSA. The average increase in the consumption of oxygen during exercise after occlusion of the fistula was 211 c.c./min./M.²BSA.

Arteriovenous oxygen differences were markedly narrowed in 5 patients and slightly narrowed in the other 2, averaging 25.7 c.c./L. for the entire group. Upon occlusion of the fistula, there was an increase in the arteriovenous oxygen difference in all patients. Similar widening in the arteriovenous oxygen difference was observed during exercise with the fistula open and with the fistula occluded.

Pulse rates were generally within normal limits, with a range from 58 to 90 per minute. Upon occlusion of the fistula, there was a decrease in heart rate in each patient; the average decrease was 10 beats per minute. Those patients with the larger fistula showed a greater bradycardic response. During exercise with the fistula open, the heart rate was increased in every patient; the average increase was 9 beats per minute. This uniform increase in rate was not observed when the exercise was repeated after occlusion of the fistula. In 1 patient (M. R.) the pulse rate decreased from 90 to 80. In 1 patient (T. S.) the pulse rate did not show any change. In the other 3 patients the pulse rate rose normally.

Stroke index was increased in each patient; it ranged from 55 to 265 c.c./beat/M.²BSA, with an average for the group of 95 c.c./beat/M.²BSA, as compared to a normal value of 42.5 ± 3.8 c.c./beat/M.²BSA. After occlusion of the fistula, the stroke index decreased to normal in 5 of the patients. During exercise with the fistula open, a decrease was observed in 3 patients in whom the cardiac index showed a decrease. The other 4 patients showed slight to marked increase in the stroke index. After occlusion of the fistula, exercise caused a decrease in stroke volume in 4 patients, and an increase in 1 patient.

TABLE II. HEMODYNAMIC DATA DURING REST AND EXERCISE

NAME, SEX, AGE, M.²BSA	EXPERIMENTAL CONDITION	OXYGEN CONSUMPTION (C.C./MIN./M.²BSA)	A-V OXYGEN DIFFERENCE (C.C./L.)	CARDIAC INDEX (L./MIN./M.²BSA)	HEART RATE (PER MINUTE)	STROKE INDEX (C.C./MIN./M.²BSA)	PRESSURES (MM. Hg)											CARDIAC WORK INDEX (KG.M./BSA)	STROKE WORK INDEX (GM.M./BSA)	RESISTANCES (DYNES/SEC./CM.⁻⁵)	
							BRACHIAL ARTERY			PULMONARY ARTERY			RIGHT VENTRICLE			RIGHT AURICLE	PULMONARY CAPILLARY			TOTAL PERIPHERAL	PULMONARY ARTERIOLAR
							S	D	M	S	D	M	S	P.D.†	E.D.‡	M	M				
M.R.	R-O*	152	20.5	7.4	90	82	103	51	72	37	19	24	38	3	11	4	2	7.4	82	522	158
Female	R-C	145	43.0	3.4	80	43	130	61	88	19	10	16	—	–	–	—	2	4.2	53	1,410	224
44	E-O	276	41.5	6.6	94	71	128	64	84	39	19	16	—	–	–	—	5	7.6	81	680	89
1.48	E-C	215	44.9	4.8	80	60	126	60	89	21	12	16	—	–	–	—	3	5.9	74	1,000	146
E.H.	R-O	182	8.0	23.9	90	265	137	65	80	23	15	19	30	3	9	9	15	21.2	235	156	8
Male	R-C	164	24.0	6.9	60	113	140	80	95	20	10	16	—	–	–	—	12	8.1	135	620	26
31	E-O	245	31.0	8.0	94	84	140	70	95	—	—	22	—	–	–	—	16	9.0	96	535	34
1.79	E-C	—	—	—	—	—	—	—	—	—	—	—	—	–	–	—	—	—	—	—	—
T.S.	R-O	120	24.8	4.9	86	57	138	80	98	19	7	12	19	0	2	2	6	6.5	76	792	50
Male	R-C	113	38.0	3.0	80	38	138	90	100	16	9	12	—	–	–	—	5	4.0	50	1,332	93
45	E-O	386	82.4	4.8	86	56	151	99	109	30	15	20	—	–	–	—	5	7.0	82	920	126
2.03	E-C	419	90.9	4.6	86	54	139	96	103	23	13	17	—	–	–	—	6	6.5	76	876	94

L.T.	R-O	144	27.4	5.3	76	70	125	59	70	24	6	13	26	2	2	2	4	5.0	66	576	74
Male	R-C	124	40.9	3.1	67	46	130	80	93	19	6	12	—	–	–	—	3	3.9	58	1,326	129
49	E-O	277	39.1	7.1	86	82	135	65	94	33	18	23	—	–	–	—	7	8.8	102	578	98
1.84	E-C	271	55.6	4.9	87	56	159	96	122	25	8	13	—	–	–	—	7	8.0	92	1,096	53
H.J.	R-O	154	30.0	5.2	76	68	103	65	78	23	8	12	20	0	5	3	7	5.3	70	608	43
Male	R-C	—	—	—	—	—	—	—	—	—	—	—	—	–	–	—	—	—	—	—	—
31	E-O	502	54.8	9.1	100	91	118	68	96	24	10	13	—	–	–	—	7	10.3	103	432	29
1.81	E-C	—	—	—	—	—	—	—	—	—	—	—	—	–	–	—	—	—	—	—	—
P.A.	R-O	130	35.2	3.7	58	64	185	60	92	82	33	50	83	4	4	13	27	3.5	60	931	245
Male	R-C	137	45.1	3.1	54	57	170	67	98	44	18	24	—	–	–	—	19	3.5	65	1,260	65
63	E-O	226	55.7	4.0	62	65	200	70	110	96	32	53	—	–	–	—	19	5.3	85	1,065	234
2.03	E-C	179	59.7	3.0	66	45	—	—	—	95	33	52	—	–	–	—	22	—	—	—	393
W. R.	R-O	154	33.7	4.6	83	55	116	76	93	15	5	9	22	4	5	2	5	5.8	70	888	38
Male	R-C	268	44.0	3.9	81	48	135	83	105	14	5	8	—	–	–	—	4	5.8	71	1,148	44
16	E-O	657	94.1	7.2	100	72	159	78	102	21	8	13	—	–	–	—	8	9.7	97	610	30
1.84	E-C	709	98.8	7.2	94	76	173	81	116	22	10	13	—	–	–	—	8	11.1	118	700	30
Mean Values	R-O	148	25.7	7.9	80	95	130	65	83	32	13	20	—	–	–	—	9.4	7.8	94	639	88
	R-C	154	39.2	3.9	70	58	140	77	97	22	10	15	—	–	–	—	7.5	4.9	72	1,183	97
	E-O	379	56.9	6.7	89	74	147	74	99	41	17	23	—	–	–	—	9.6	8.2	92	689	91
	E-C	359	70.0	4.9	83	58	149	83	108	37	15	22	—	–	–	—	9.2	7.9	90	918	143

***R-O: Rest—fistula open. R-C: Rest—fistula closed. E-O: Exercise—fistula open. E-C: Exercise—fistula closed.**
†Protodiastolic.
‡End-diastolic.

The left ventricular work index was high in all patients except one; it ranged from 3.5 to 21.2 Kg.M./min./M.^{2}BSA, with an average of 7.8 Kg.M./min./M.^{2}BSA, as compared with a normal value of 4.03 ± 0.45 Kg.M./min./M.^{2}BSA. Upon occlusion of the fistula, a decrease to normal levels was observed in each patient, with the exception of one (E.H.). During exercise with the fistula open, it did not change significantly in 2 patients, decreased by one half in 1 patient (E.H.), and increased in the other patients. The left ventricular work index was calculated in 4 patients during exercise after occlusion of the fistula. A decrease in 1 patient (M.R.) and an increase in 2 patients (W.R., L.T.) was observed, whereas the other patients did not show significant change.

Two patients (E.H., P.A.) had elevated pulmonary "capillary" mean, right atrial mean, and right ventricular end-diastolic pressures. The other patients showed normal pressures. On occlusion of the fistula, the pulmonary "capillary" pressures did not show any significant change in 5 patients, but decreased slightly in the 2 in whom there was an elevation of the pressures in the control states. During exercise with the fistula open, the "capillary" pressures increased slightly in 4 patients, decreased in 2, and did not change in 1. Identical response, individually and collectively, was observed during exercise after occlusion of the fistula. Slight to moderate pulmonary hypertension was present in 2 patients (M.R., P.A.), one of whom was known to be in left heart failure. Upon occlusion of the fistula, the pressures decreased slightly in 5 patients, and markedly in 1 (P.A.). During exercise with the fistula open, these pressures increased slightly in all patients. The same results were obtained in 4 patients during exercise after occlusion of the fistula, but 1 patient (M.R.) showed a decrease in pulmonary arterial pressure. The brachial arterial systolic pressures were within normal limits in all except 1 patient who was known to be hypertensive. Diastolic pressures were normal in 2 and decreased in 5 patients. Upon occlusion of the fistula, the brachial arterial systolic pressures increased slightly in every patient, with the exception of the one who had hypertension. Diastolic pressures increased significantly, with a consequent slight decrease in the average pulse pressure. During exercise with the fistula open and occluded, these pressures increased in every patient.

In each of the patients, the total peripheral resistance was below the normal value; it averaged 639 dynes/sec./cm.$^{-5}$ for the group, as compared with the normal value of 1,305 ± 29.1 dynes/sec./cm.$^{-5}$. Upon occlusion of the fistula, the resistance increased in every patient, and reached a normal level in 5. On exercise with the fistula open, the total peripheral resistance decreased in 3, but increased in 3 others who had a fall in output, and in the patient (M.R.) who had an increase in filling pressure with the exercise. After occlusion of the fistula, when the exercise was repeated, the total peripheral resistance increased in 3 patients and fell in 1. Pulmonary arteriolar resistance showed the same directional change as peripheral resistance on exercise and on occlusion of the fistula.

DISCUSSION

Despite the heterogeneity of response to exercise in these 7 patients a certain pattern has been observed which is based on the hemodynamic state of the patients at the time and was elucidated by studies after occlusion of the fistula.

Thus, a high cardiac output at rest existed, unless heart failure supervened, and could be reduced by occlusion of the fistula. The supernormal response to exercise, alleged to exist in hyperkinetic states, was observed if the resting output was above 4.6 L./min./M.^{2}BSA. Similar responses of abnormally high cardiac output have been reported in cases of anemia only if the resting level was above 4.6 L./min./M.^{2}BSA.[8] The most unusual aspect of this study was the substantial decline in cardiac output in 3 patients during exercise, in the absence of associated heart failure as judged by ventricular filling pressures. Exercise was repeated after occlusion of the fistula, with a decline in cardiac output similar to that occurring with exercise when the fistula was open. These findings suggest that a somewhat similar phenomenon occurred in the open fistula during exercise, that is, the fistula was partially occluded by leg movement. The occurrence of this phenomenon depended on, and varied with, the size of the fistula, its location, and the type of exercise in which the patient participated. The mechanism producing occlusion of the fistula during exercise is obscure. Two factors might possibly lead to occlusion: the contraction of the muscles of the exercising leg could mechanically occlude the fistula, or the arteriovenous pressure gradient could decrease so much that the flow through the fistula ceased and flow was directed to normal pathways. During exercise, muscular pressure increases, but this elevation of tissue tension could not bring the venous pressure to the arterial level,[9,10] and, therefore, could not explain the large decrease in the cardiac output observed in some of our patients. The first possibility, i.e., mechanical occlusion by the exercising muscle, is, therefore, more probable than changes in arteriovenous pressure gradients. In addition, there is arteriolization of the venous channels and thinning of the walls of the arterial channels in the area of the fistula in patients with chronic arteriovenous fistula, and this pathologic process could facilitate the mechanical occlusion of the fistula during exercise.

According to widely accepted views, increased venous return due to pumping action of skeletal muscles and the decreased peripheral resistance is the cause of the increased cardiac output observed during exercise.[11] This increase in cardiac output can result either from an acceleration of heart rate[12] or from an elevation of stroke volume, or from both.[13] A well-trained athlete responds to exercise with an increase in the stroke volume rather than an acceleration of the heart rate.[14] The resting hemodynamics of our 7 patients with chronic arteriovenous fistula showed that the high cardiac output was the result of an increased stroke volume while the heart rate was normal. During exercise, the cardiac output in the 3 uncomplicated cases increased both through increased stroke volume and tachycardia. Similar results have been reported in other hyperkinetic states during exercise and in physically trained man during successive exercise.[15] Hence, it would appear that further increasing venous return to the chronically loaded, unfailed heart of patients with states of high cardiac output is accommodated not only by tachycardia but, additionally, by increments of stroke volume, in keeping with the mode of increase in cardiac output observed in the resting hyperkinetic state. In the 3 patients in whom cardiac output decreased during exercise, as a result of spontaneous temporary occlusion of the fistula, stroke volume decreased linearly with the cardiac output, whereas the heart rate increased slightly or stayed at the same level. Thus, in all patients, cardiac output tended to parallel stroke volume rather than heart rate.

In all 7 patients, under the various experimental situations, no correlation was found between the filling pressure of the left ventricle, as measured by pulmonary "capillary" pressure, and the stroke volume or stroke work. Since, in this series, the filling pressures were not related to the magnitude of the stroke volume, an increase in the latter could be explained either by an increase in the diastolic volume without change in filling pressures, or by a more complete emptying of the ventricles due to increased ventricular contractility or normal ventricular contractility with emptying of the ventricle as a result of low peripheral vascular resistance. The increase in the size of the heart that was observed in all but one of these patients would suggest that their diastolic volume was increased at rest. Whether or not, during exercise or rest, a more complete emptying of the ventricles contributed to the increase in stroke volume in these patients is only a matter of conjecture.

SUMMARY

Hemodynamic studies were carried out in 7 patients with arteriovenous fistulas, during rest and exercise, when the fistula was open and closed. A high cardiac output existed in all patients during rest, unless congestive heart failure was present. A uniform decrease in cardiac output was observed upon occlusion of the fistula. Two patients increased their cardiac output supernormally on exercise. Muscular occlusion of the fistula was postulated in 3 patients without heart failure, in whom a decline in cardiac output occurred during exercise. Correlation between the filling pressures of the left ventricle and stroke volume could not be made in the various experimental situations studied.

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Indicator-Dilution Curves in Valvular Heart Disease: After Injection of Indicators Into the Pulmonary Artery and the Left Ventricle

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Indicator-dilution curves are being used extensively in many medical centers for the diagnosis of cardiovascular disease. However, there has been scanty information in the literature regarding the detailed analysis of the dilution curves recorded after injection of indicator into the right and left sides of the heart in patients with valvular heart disease. It is the purpose of this paper to present the statistical data on indicator-dilution curves recorded after the injection of indicator into the pulmonary artery and the left ventricle in 7 healthy subjects and in a series of 105 patients with valvular heart disease. Arterial dilution curves recorded after the injection of the indicator into the pulmonary artery are hereinafter referred to as PA curves, and those recorded after injection into the left ventricle are referred to as LV curves. Particular attention is given to (a) the blood volume between the site of injection (pulmonary artery or left ventricle) and the site of sampling (femoral artery), and (b) the contour and time-concentration components of the indicator-dilution curves.

CLINICAL MATERIAL

Series A: Healthy Subjects and Patients in Whom PA Curves Were Recorded.—Indicator-dilution curves were recorded in 7 healthy subjects, and the data were used to serve as control values. Dilution curves were also obtained in 89 patients with valvular heart disease. According to the clinical, physiologic, and, in many instances, operative findings, these 89 patients were grouped as follows: *Subgroup 1:* 41 patients with pure or predominant mitral stenosis; *Subgroup 2:* 24 patients with pure or predominant mitral insufficiency; *Subgroup 3:* 8 patients with predominant aortic stenosis; and *Subgroup 4:* 16 patients with predominant aortic insufficiency.

Series B: Patients in Whom LV Curves Were Recorded.—Thirty-six patients with various types of valvular lesions were included, in 25 of whom PA curves were also obtained simultaneously or from 10 to 15 minutes apart. As in Series A, these 36 patients were grouped according to their

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predominant lesions as follows: *Subgroup 1:* 8 patients with predominant mitral stenosis; *Subgroup 2:* 5 patients with predominant mitral insufficiency; *Subgroup 3:* 10 patients with predominant aortic stenosis; and *Subgroup 4:* 13 patients with predominant aortic insufficiency. Twenty of the 36 patients were also included in Series A.

METHODS

Apparatus, Indicators, and Recording of Dilution Curves.—The apparatus for recording radioactivity of iodinated (I^{131}) human serum albumin (hereinafter referred to as I^{131} HSA) in arterial blood was similar to that for the precordial recording described in a previous paper.[1] In order to sample and record arterial blood, we modified our method as follows, making it similar to that described by MacIntyre and Pritchard.[2]

The equipment included a scintillation detector, a count rate computer,* and a direct-writing Rectiriter.† The detector was a cylindrical thallium-activated sodium-iodide crystal, 4.5 cm. in diameter and 3.8 cm. in length, coupled to a photomultiplier tube and shielded by a cylinder of lead 2.5 cm. in thickness and 10.2 cm. in length. A plastic tube was passed through a hole drilled along a diameter of the crystal. One end of the tube was connected to an 18-G Cournand arterial needle, and the other end to a 30-ml. or 50-ml. syringe mounted on a Colson constant flow system‡ (hereinafter referred to as pump). The total volume of the tube and the sampling needle was 2.5 ml., the volume of the tube from the tip of the needle to the center of the crystal was 1.3 ml., and the actual volume of the tube inside the crystal was 0.28 ml.

The pump was regulated to withdraw approximately 40 ml. per minute. The signal from the detector was fed into the count rate computer, and the radioactivity of I^{131} HSA was summed for each second and inscribed on a single-channel Rectiriter at a paper speed of 12 inches per minute.

In the latter part of our study a Colson densitometer‡ was added in series with the scintillation counter for quantitative recording of Tricarbocyanine dye II (hereinafter referred to as Cardiogreen§). The internal volume of the densitometer cuvette was 0.04 ml., and the volume between the tip of the needle and the cuvette was 2.5 ml. The dilution curves of I^{131} HSA and Cardiogreen were recorded simultaneously on a two-channel Rectiriter (Fig. 1). In all curves, correction was made for the time required for injection and for the blood to travel from the tip of the arterial needle to the center of the scintillation counter and of the cuvette.

The syringe containing each injected dose of either I^{131} HSA or Cardiogreen was carefully weighed before and after the injection, and the net weight was used for subsequent calculation. A standard solution of I^{131} HSA was also weighed for a given patient.

In patients of Series A, the PA curves were recorded when a rapid injection of one or both indicators was made through a cardiac catheter, followed by a rapid 5-ml. saline flush, into the main pulmonary artery. In patients of Series B, the LV curves were inscribed after rapid injection of I^{131} HSA through a 19- or 21-T gauge needle into the left ventricle according to the percutaneous technique of Brock.[3,4] In most patients of Series B, PA curves were recorded either simultaneously with LV curves after the injection of Cardiogreen or successively, after the injection of I^{131} HSA.

In 85 patients of Series A, and in 15 patients of Series B, during the inscription of the PA or LV curves, cardiac output was determined also by nearly simultaneous Fick procedure.

Terms and Symbols for Time and Concentration Components.—The definitions and symbols of all time-concentration components are basically those described by Wood and Swan.[5] When the dilution curve was plotted semilogarithmically, the reciprocal of the downslope of the curves[6] was defined as follows:

$$1/S = \frac{t_2 - t_1}{\log C_1 - \log C_2}$$

where (C_1, t_1, and C_2, t_2) represented the coordinates of two points on the straight line downslope. If C_1 and C_2 were chosen one logarithmic cycle apart (10,000 and 1,000 CPM, or 1,000 and

*Model 118 B, Radiation Instrument Development Laboratory, Chicago, Ill.
†Obtained from Texas Instruments, Inc., Houston, Tex.
‡Obtained from Gilford Instrument Laboratories, Inc., Oberlin, Ohio.
§Obtained from Hynson, Westcott and Dunning, Inc., Baltimore, Md.

100 CPM), the denominator became 1, and 1/S was numerically equal to the difference in time in seconds between points C_1 and C_2.

Blood Volume and Cardiac Output Determination.—Only the dilution curves recorded after the injection of I^{131} HSA were used for the estimation of blood volume and cardiac output.

Total blood volume (TBV): Total blood volume was calculated as follows:

$$\text{TBV (in ml.)} = \frac{W_p}{W_s} \cdot \frac{CPM_s}{CPM_e} \cdot 1{,}000$$

where W_p = weight of the dose of I^{131} HSA given to the patient; W_s = weight of the dose of the diluted standard; CPM_s = CPM/ml. of the diluted standard; CPM_e = CPM/ml. of the patients' blood sample at 10-minute equilibrium point; and 1,000 = volume of diluted standard in ml. It was assumed that, at each determination, the hematocrit of the blood sample did not differ significantly from the total body hematocrit.

Cardiac output: Cardiac output was determined as follows:

$$\text{C.O.} = \frac{C_e \cdot \text{TBV} \cdot 60}{A}$$

where C.O. = cardiac output (ml./min.); C_e = equilibrium concentration (CPM/L.); TBV = total blood volume (ml).; and A = the area under the extrapolated primary circulation curve replotted on a linear scale and measured by planimeter (CPM/L. × sec.).

"Central" blood volume and its compartments: "Central" blood volume (CBV) and its compartments were estimated by the Stewart-Hamilton formula.[7] The volume between site of injection and site of sampling was the product of the mean transit time in seconds between the two sites and the cardiac output per second. Thus:

(1) PA to FA Volume = C.O. × T_M (PA to FA)
(2) LV to FA Volume = C.O. × T_M (LV to FA)
(3) PA to LA Volume = (1) − (2)

where PA = pulmonary artery; FA = femoral artery; LV = left ventricle; LA = left atrium; C.O. = cardiac output in ml./sec.; and T_M = mean transit time in seconds.

RESULTS

Tables I and II present the statistical data of the forward cardiac index,* total and "central" blood volumes, and time-concentration components derived from the PA curves in patients of Series A. In Table III are shown similar data with additional information regarding compartments of "central" blood volume derived from the LV curves in patients of Series B.

Forward Cardiac Index (CI).—In patients of Series A, with the exception of the subgroup of patients with aortic stenosis, the average cardiac index was significantly lower than that in the healthy subjects, either by the Fick procedure or by the indicator-dilution curves. However, no significant difference in the average cardiac index was observed between any two subgroups.

In 24 patients, successive determinations of the cardiac index by dilution curves were made from 15 to 20 minutes apart, in order to show the reproducibility of the results. No significant difference between the first and second determinations was observed.

Blood Volume.—

Patients of Series A: The mean total blood volume (TBV) in 7 subjects without cardiovascular disease was 2,658 ml./M.^{2}. The mean TBV in patients

*Cardiac index = cardiac output per square meter of body surface area.

TABLE I. STATISTICAL DATA OF FORWARD CARDIAC INDEX AND TOTAL AND "CENTRAL" BLOOD VOLUMES DERIVED FROM INDICATOR-DILUTION CURVES FOLLOWING INJECTION OF I^{131} HSA INTO THE PULMONARY ARTERY

SUBGROUP (SERIES A)	NUMBER OF CASES	FORWARD CARDIAC INDEX (L./M.²/MIN.)				BLOOD VOLUME (ML./M.²)					
		FICK PROCEDURE		DILUTION CURVE		TOTAL (TBV)		"CENTRAL" (CBV)		CBV/TBV × 100	
		MEAN	S.E.	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.
Healthy subjects	7	4.25	0.32	4.37	0.34	2,658	132	617	35	23.4	1.44
Mitral stenosis	41	3.05	0.11	3.17	0.13	2,912	58	714	20	24.6	0.77
Mitral insufficiency	24	2.88	0.20	2.86	0.14	3,065	140	766	37	25.1	0.98
Aortic stenosis	8	3.66	0.38	3.47	0.40	2,896	114	744	54	26.0	2.10
Aortic insufficiency	16	3.09	0.15	3.07	0.18	3,218	166	795	60	24.5	1.15

S.E.: Standard error. TBV: Total blood volume. CBV: "Central" blood volume.

TABLE II. STATISTICAL DATA OF TIME-CONCENTRATION COMPONENTS OF THE INDICATOR-DILUTION CURVES FOLLOWING INJECTION OF I^{131} HSA INTO THE PULMONARY ARTERY

SUBGROUP (SERIES A)	NUMBER OF CASES	TIME COMPONENTS (SECONDS)										1/S	
		T_A		T_B		T_{PC}		T_M		T_D			
		MEAN	S.E.	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.
Healthy subjects	7	5.3	0.19	3.9	0.15	9.1	0.34	9.6	0.41	12.9	0.90	5.9	0.30
Mitral stenosis	41	7.9	0.30	5.7	0.31	13.5	0.45	14.9	0.56	24.2	1.43	11.5	0.81
Mitral insufficiency	24	8.4	0.57	6.7	0.49	15.1	0.94	17.7	1.22	37.5	4.10	18.3	2.33
Aortic stenosis	8	8.5	0.62	5.8	0.48	14.3	1.00	14.8	1.00	20.0	1.59	10.2	1.06
Aortic insufficiency	16	8.6	0.65	6.5	0.52	15.1	1.10	17.5	1.50	37.2	6.60	19.5	3.91

T_A: Appearance time. T_B: Build-up time. T_{PC}: Peak concentration time. T_M: Mean transit time. T_D: Disappearance time. 1/S: Reciprocal of downslope. S.E.: Standard error.

with mitral stenosis and in those with aortic stenosis showed no significant difference from that observed in healthy subjects. On the other hand, in patients with mitral insufficiency and in those with aortic insufficiency the mean TBV was significantly higher than the mean normal value ($p < 0.05$).

No correlation was found between TBV and CI, although a highly significant correlation was found between TBV and CBV ($p < 0.01$).

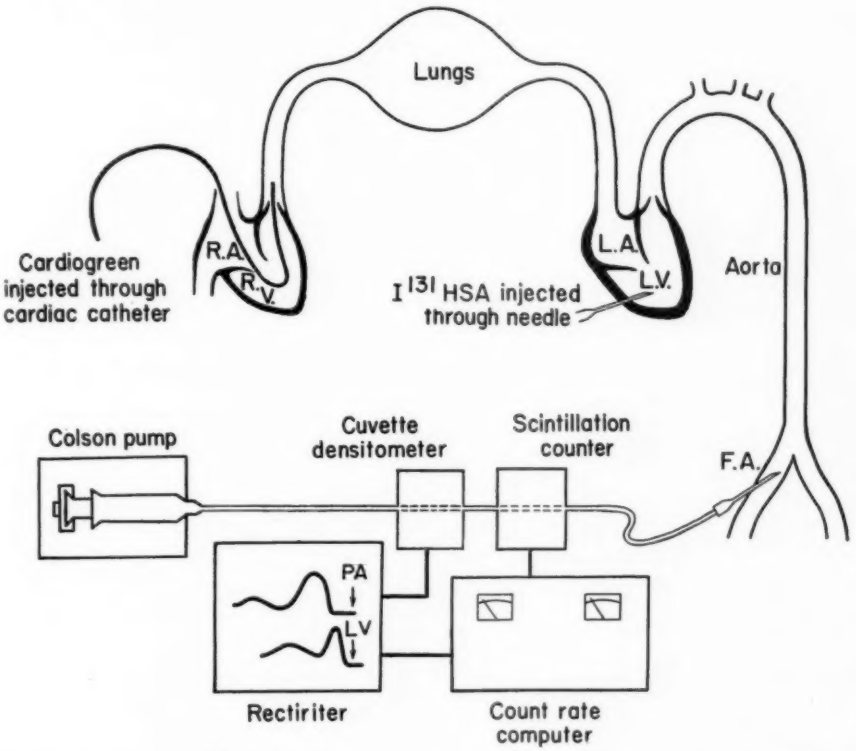

Fig. 1.—Schematic diagram showing sites of injection of two indicators, sampling of arterial blood, and apparatus for recording dilution curves.

The mean CBV in 7 healthy subjects was 617 ml./M.^{2}. Except for the subgroup of patients with aortic stenosis, which included only 8 patients, the mean CBV in each subgroup of patients was significantly greater than that in normal subjects ($p < 0.05$). However, there was no significant difference between the mean of any two subgroups. With regard to comparable functional disability, the CBV was usually greater in patients with valvular insufficiency than in those with valvular stenosis.

The difference between the first and second determinations of CBV was less than 100 ml./M.^{2} in 22 of 24 patients in whom two successive indicator-dilution curves were recorded from 15 to 20 minutes apart. The mean ratios of CBV to TBV were remarkably constant, ranging from 23.4 to 26.0 per cent in all subgroups. No sharp distinction could be made between any two subgroups.

Compartmentation of "central" blood volume in patients of Series B. LV to FA volume: As shown in Table III, the mean LV to FA volume in patients with

TABLE III. COMPARTMENTATION OF "CENTRAL" BLOOD VOLUME AND TIME-CONCENTRATION COMPONENTS DERIVED FROM INDICATOR-DILUTION CURVES FOLLOWING INJECTION OF I^{131} HSA INTO THE LEFT VENTRICLE

SUBGROUP (SERIES B)	CASE NUMBER	"CENTRAL" BLOOD VOLUME (ML./M.²)		TIME COMPONENTS (SECONDS)					1/S
		PA TO LA VOLUME	LV TO FA VOLUME	T_A	T_B	T_{PC}	T_M	T_D	
Mitral stenosis	1	373	162	2	2	4	5	11	4.7
	2	489	255	2	2	4	5	13	4.9
	3	528	348	3	4	7	9	19	7.9
	4	489	353	3	4	7	8	23	8.8
	5	292	385	2	3	5	6	11	4.1
	6	246	387	3	3	6	7	17	7.5
	7	—	445	3	3	6	7	14	5.5
	8	253	567	4	3	7	10	20	8.6
Mean ± S.E.		381 ± 42	363 ± 42	2.8 ± 0.25	3.0 ± 0.25	5.8 ± 0.46	6.5 ± 0.61	16 ± 1.50	6.5 ± 0.68
Mitral insufficiency	9	413	223	3	3	6	8	22	8.1
	10	335	297	2	2	4	5	15	6.0
	11	205	375	3	2	5	6	18	7.4
	12	348	468	5	3	8	11	25	11.8
	13	—	553	4	4	8	10	23	7.5
Mean ± S.E.		325 ± 36	385 ± 56	3.4 ± 0.51	2.8 ± 0.37	6.2 ± 0.79	8.0 ± 1.18	20.6 ± 1.78	8.2 ± 0.97

Aortic stenosis	14	403	232	2	3	5	6	18	7.4
	15	328	301	2	3	5	6	14	5.0
	16	—	339	3	5	8	9	20	8.0
	17	454	346	2	3	5	8	19	8.4
	18	253	356	3	4	7	8	18	7.1
	19	530	432	2	3	5	8	15	7.3
	20	560	455	4	4	8	9	14	4.7
	21	—	462	3	4	7	8	18	10.0
	22	—	513	3	4	7	9	14	5.5
	23	—	754	4	5	9	11	25	13.8
Mean ± S.E.		371 ± 40	419 ± 46	2.8 ± 0.25	3.8 ± 0.22	6.6 ± 0.47	8.2 ± 0.44	17.5 ± 0.11	7.7 ± 0.87
Aortic insufficiency	24	121	330	4	4	8	10	24	9.7
	25	464	346	3	6	9	11	51	23.2
	26	171	361	4	5	9	11	22	8.5
	27	315	381	3	4	7	11	31	13.0
	28	306	406	3	4	7	8	21	9.4
	29	413	414	3	5	8	9	26	10.1
	30	510	440	2	3	5	7	15	8.2
	31	—	452	2	4	6	8	15	6.2
	32	—	540	4	8	12	15	57	28.0
	33	—	552	3	4	7	8	28	12.1
	34	358	580	4	4	8	10	19	8.2
	35	—	634	3	7	10	13	63	37.0
	36	—	747	3	6	9	14	79	30.0
Mean ± S.E.		332 ± 37	476 ± 33	3.2 ± 0.19	4.9 ± 0.39	8.1 ± 0.50	10.4 ± 0.69	34.7 ± 5.5	15.7 ± 2.82

PA to LA: Pulmonary artery to left atrium. LV to FA: Left ventricle to femoral artery. Other abbreviations as in Table II.

aortic insufficiency was significantly greater than in those with mitral stenosis ($p < 0.05$). No significant difference was found in the LV to FA volume between any other two subgroups.

The mean PA to LA volume varied between 325 and 381 ml./M.^{2} in all four subgroups. There was no significant difference in the mean value between any two subgroups.

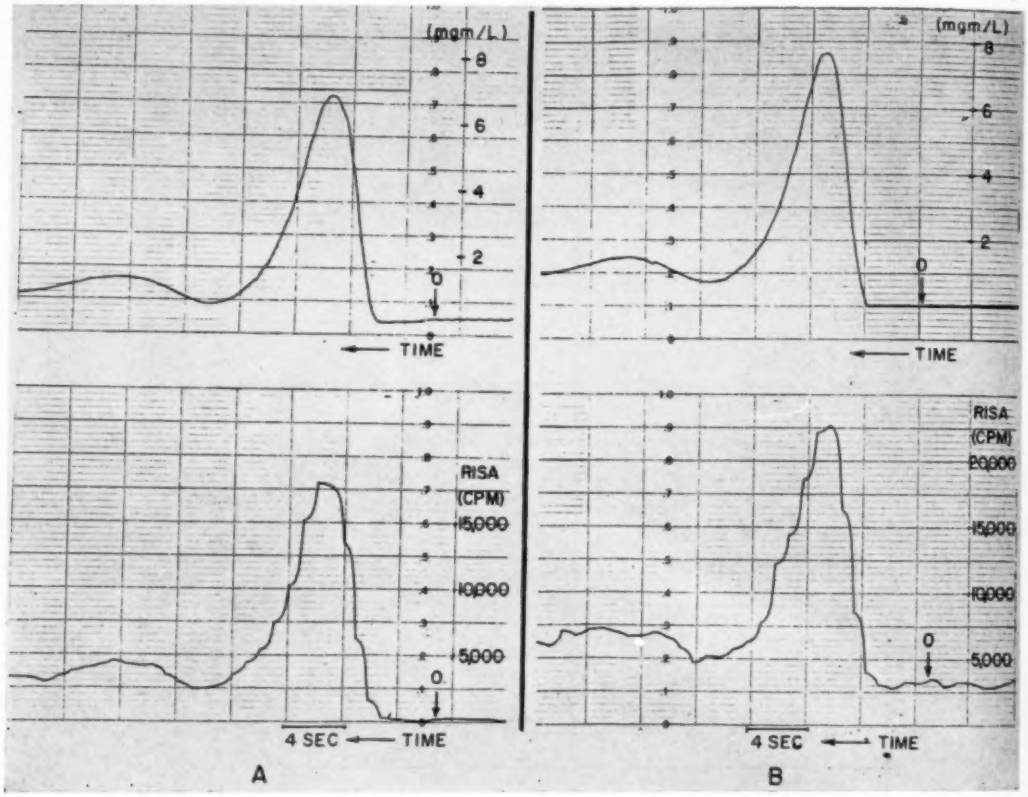

Fig. 2.—Indicator-dilution curves recorded in simultaneous pairs from the femoral artery after injections of a mixture of Cardiogreen (*upper tracings*) and I^{131} HSA (*lower tracings*) into the pulmonary artery of a healthy subject. The tracings in the right panel were obtained about 15 minutes after those in the left panel. Note the similarity of the curves recorded with two different indicators, and also the reproducibility of the curves, with a steep ascent, sharp peak, and a rapid, smooth descent. In this and subsequent graphs the arrow below 0 indicates the corrected time of injection.

General Contour and Time Components of Indicator Curves.—

PA curves in patients of Series A: The PA curves recorded in 7 healthy subjects were characterized by a steep ascent, a sharp peak, and a smooth, rapid descent. In each subject the general contour and time components of two or more dilution curves recorded under similar conditions were practically the same (Fig. 2). The appearance and build-up times (T_A and T_B) were each 6 seconds or less, and the disappearance time (T_D) was 16 seconds or less. The peak concentration time (T_{PC}) and mean transit time (T_M) were 12 seconds or less. The reciprocal of downslope (1/S) was 6.7 or less. These values will be considered as normal in the following discussion.

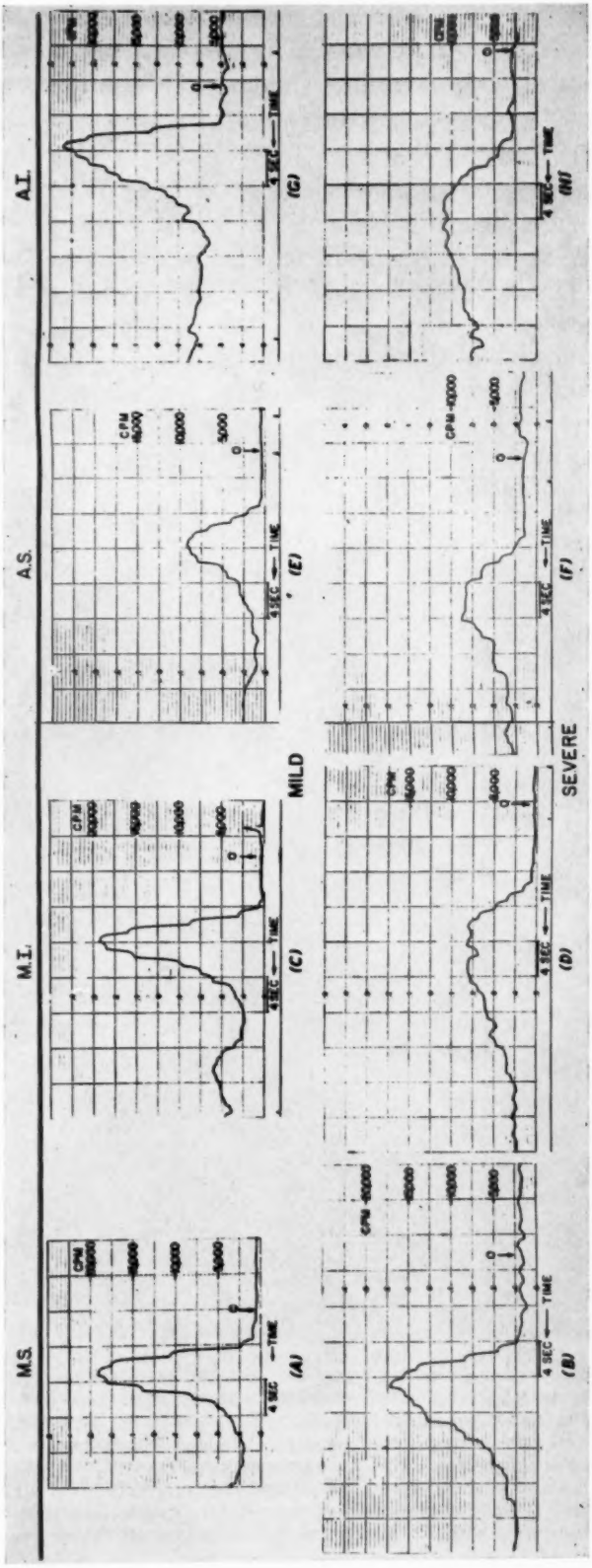

Fig. 3.—Representative arterial indicator-dilution curves recorded after injection of I^{131} HSA into the pulmonary artery of patients with mitral stenosis (*M.S.*), mitral insufficiency (*M.I.*), aortic stenosis (*A.S.*), and aortic insufficiency (*A.I.*). In the upper row are the curves (*A*, *C*, *E*, and *G*) obtained from patients with mild lesions. In the lower row are the curves (*B*, *D*, *F*, and *H*) from patients with severe lesions. The dose of I^{131} HSA injected was approximately the same in each case. Note the similarity of the contour of the indicator-dilution curves in patients with mild stenosis and in those with mild mitral insufficiency.

As compared with the mean values in healthy subjects, there was a significant prolongation of T_A, T_B, T_{PC}, T_M, T_D, and an increase in 1/S in patients of all four subgroups. However, there was no significant difference in mean T_A, T_B, T_{PC}, and T_M between any two subgroups, except for the longer T_M in patients with mitral insufficiency than in those with mitral stenosis. The mean T_D and 1/S were significantly more prolonged in patients with valvular insufficiency than in those with valvular stenosis ($p < 0.01$). No significant difference was observed in the mean T_D and 1/S between patients with mitral insufficiency and those with aortic insufficiency, or between patients with mitral stenosis and those with aortic stenosis.

The general contour and all time components of the PA curves were normal in 5 patients with mitral stenosis, in 2 with mitral insufficiency, and in 1 with aortic stenosis. All 8 of these patients were considered clinically to have mild lesions, with a cardiac index of 3.50 L./min./M.^{2} or greater by both the Fick procedure and indicator-dilution curve. The "central" blood volume in all 8 of

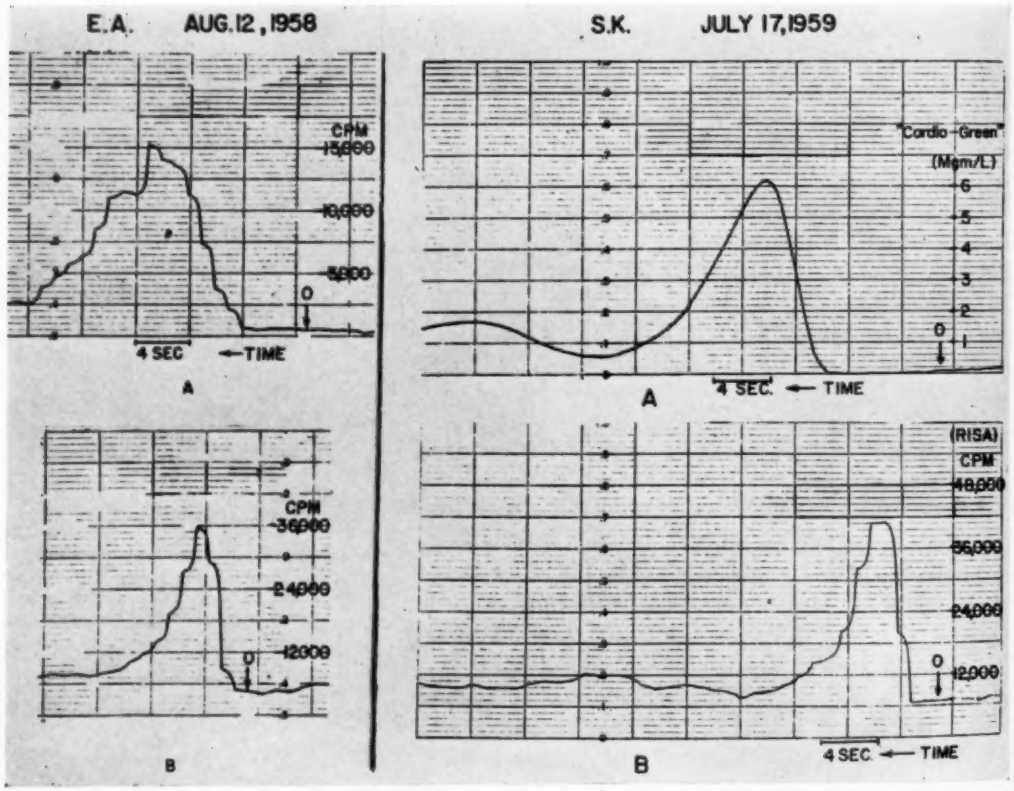

Fig. 4.—Arterial dilution curves recorded in 2 patients with mitral stenosis. In the left panel, the upper tracing was obtained after injection of I^{131} HSA into the pulmonary artery, and the lower tracing after injection of I^{131} HSA into the left ventricle. These curves were recorded approximately 15 minutes apart. In the right panel are the PA curve (*upper tracing*) and the LV curve (*lower tracing*) recorded simultaneously after injection of Cardiogreen into the pulmonary artery and I^{131} HSA into the left ventricle. The least concentration and peak concentration of systemic recirculation are easily identifiable in both curves. Note the distorted contour of the PA curves and "normal" configuration of the LV curves in both cases, when compared with PA curves recorded in a healthy subject as shown in Fig. 2.

these patients was also within normal limits. With the exception of 2 patients, all had pulmonary arterial mean pressures of 20 mm. Hg or less, and total pulmonary resistance of 250 dynes-sec.-cm.$^{-5}$ or less.

In the other patients, including all those with predominant aortic insufficiency, the general contour of the curves was grossly distorted. The distortion was characterized by a slow ascent, a rounded or flat top, and a slow descent. In patients with severe mitral or aortic insufficiency the T_D and 1/S were more markedly prolonged than were other components. Representative dilution curves from patients of each group are reproduced in Fig. 3.

LV curves in patients of Series B:

Patients with predominant mitral stenosis: LV curves were recorded in 8 patients. In 4 patients (Cases 1, 2, 5, and 7) with "pure" mitral stenosis the LV curve resembled closely the PA curve in a healthy subject but differed from the PA curve in the same patient (Fig. 4). There was no prolongation of time components, and the concentration reached a high peak lasting for only 1 second,

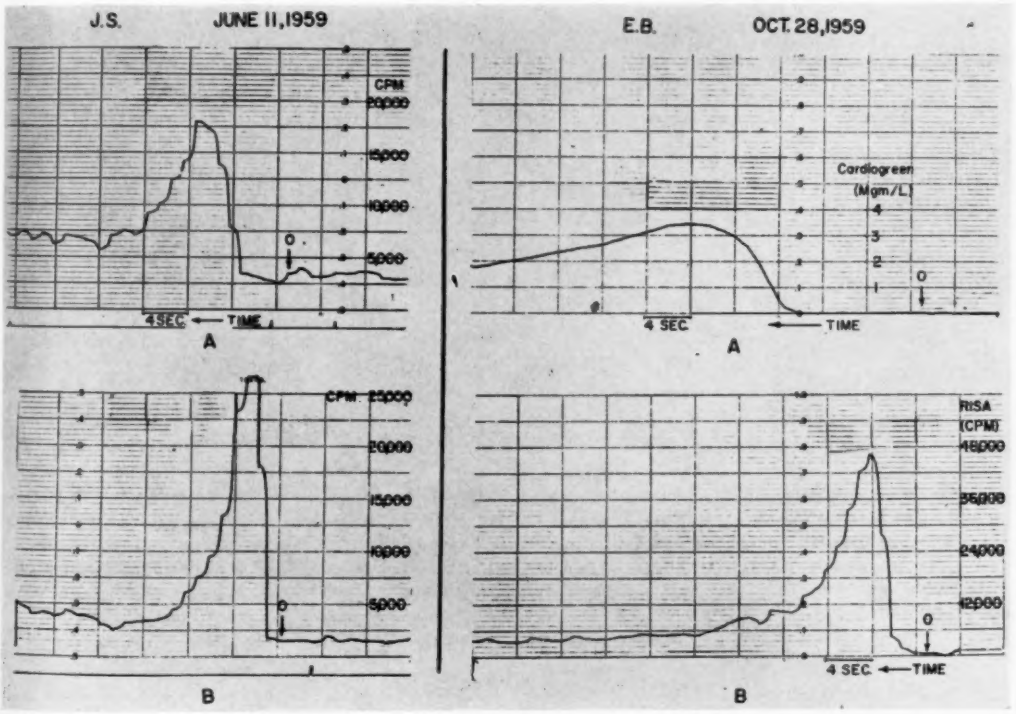

Fig. 5.—Arterial dilution curves obtained in 2 patients with mitral insufficiency. In the left panel are dilution curves from a patient with clinically mild mitral insufficiency. The upper tracing was inscribed after injection of I^{131} HSA into the pulmonary artery, and the lower tracing after injection into the left ventricle. These tracings were recorded approximately 15 minutes apart. Note slight but definite distortion of the PA curve and "normal" contour of the LV curve. In the right panel are dilution curves recorded in a patient with moderately severe mitral insufficiency. The upper tracing is a PA curve recorded after injection of Cardiogreen, and the lower tracing is an LV curve recorded simultaneously after injection of I^{131} HSA. The PA curve is grossly distorted, with prolongation of all time components and reduced peak concentration. The LV curve shows definite prolongation of disappearance time and absence of peak of systemic recirculation.

followed by a steep and smooth downslope. The T_A and T_B were 3 seconds or less, T_{PC} was 6 seconds or less, T_M was 7 seconds or less, T_D was 14 seconds or less, and 1/S was 5.5 or less. The peak of systemic recirculation was definitely identifiable. The time components of the LV curves recorded in these 4 patients were considered to be "normal."

In 4 patients with mitral stenosis who had either a history of attacks of pulmonary edema or other valvular lesions, the PA curves were grossly distorted and the LV curves showed slight prolongation of most of the time components, in comparison with those recorded in patients with uncomplicated mitral stenosis.

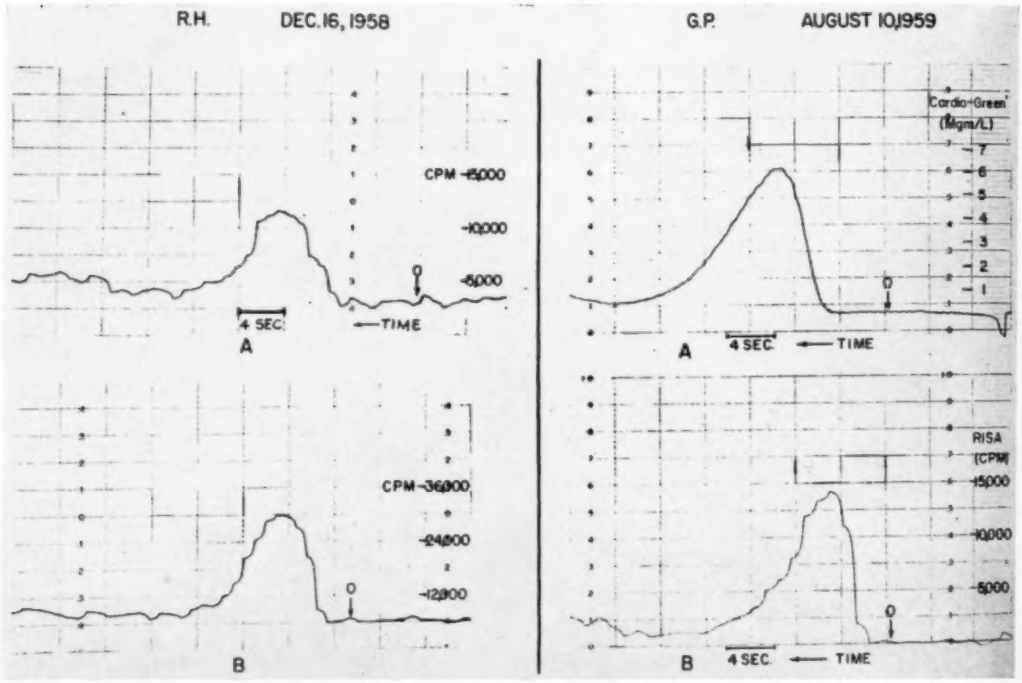

Fig. 6.—Arterial indicator-dilution curves recorded in 2 patients with aortic stenosis. The upper tracings are PA curves and the lower tracings are LV curves. In the left panel the indicator used was I^{131} HSA, and the two curves were obtained approximately 15 minutes apart. In the right panel the PA and LV curves were recorded simultaneously following injection of Cardiogreen and I^{131} HSA into the pulmonary artery and the left ventricle, respectively. Note the similarity of the PA and LV curves in each case.

Patients with predominant mitral insufficiency: Fig. 5 shows PA and LV curves recorded in a patient with a mild degree of mitral insufficiency, and in another patient with moderately severe mitral insufficiency. In the former patient the PA curve showed definite prolongation in disappearance time but there was little or no abnormality in the LV curve. In the latter patient the PA curve was grossly distorted and the LV curve showed definite prolongation of T_M and T_D, and there was no peak of systemic recirculation.

Patients with aortic valvular lesions: In patients with predominant aortic valvular lesions the countour of the LV curves was similar to that of the PA

curves. In most patients with predominant aortic stenosis (Fig. 6), both PA and LV curves showed proportionate prolongation in all time components. The top of the dilution curve in most cases was somewhat rounded.

In patients with predominant aortic insufficiency, both PA and LV curves showed prolongation of all time components and distortion of the contour. Fig. 7 shows PA and LV curves in a patient with a mild degree of aortic insufficiency and in another patient with a marked degree of aortic insufficiency. In the former patient the contour of both PA and LV curves were similar to that seen in patients with predominant aortic stenosis. In the latter patient, both PA and LV curves showed a marked prolongation in all time components, a broad top and disproportionate prolongation of T_D.

There was no significant difference in the mean T_A between any two groups. Significant prolongation of the mean T_B, T_{PC}, T_M, T_D, and 1/S was observed in the subgroup of patients with aortic insufficiency, as compared with the other

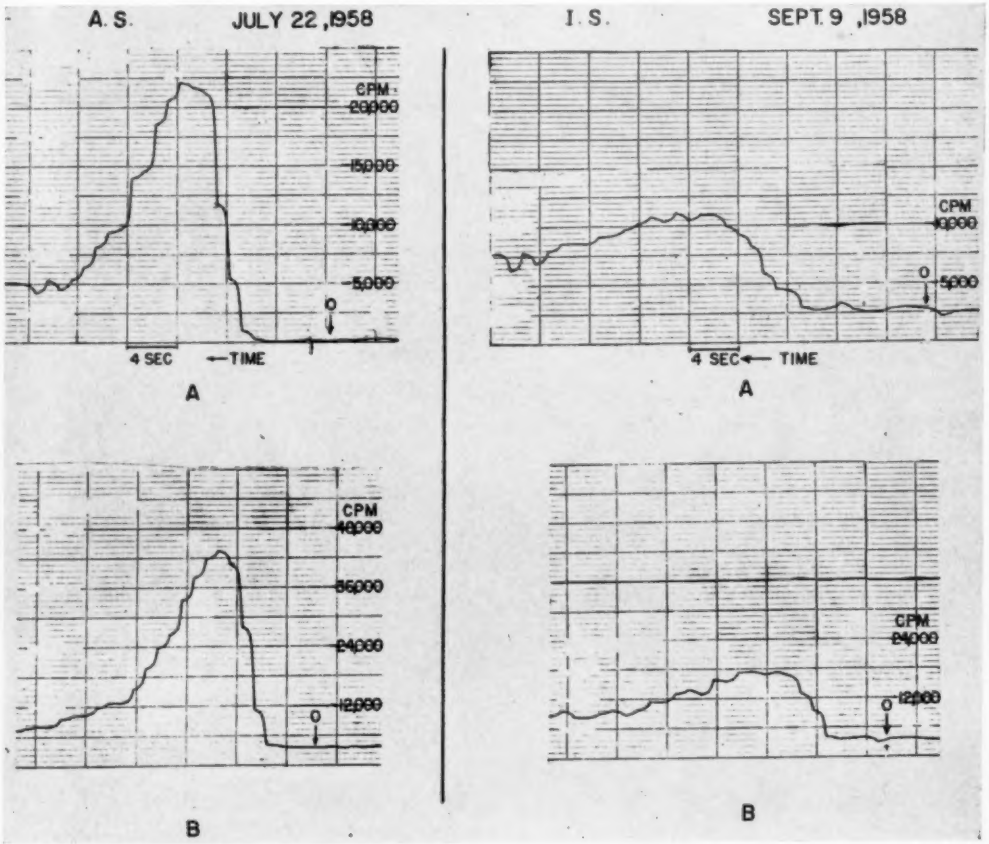

Fig. 7.—Arterial dilution curves recorded in 2 patients with aortic insufficiency. The upper tracings are PA curves and the lower ones are LV curves. I^{131} HSA was used as the indicator in each case. In the left panel the dilution curves were inscribed successively in a patient with clinically mild aortic insufficiency, and in the right panel the curves were recorded about 15 minutes apart in a patient with severe aortic insufficiency. Note the similarity of the PA and LV curves in each patient. In mild aortic insufficiency the PA and LV curves are almost identical with those recorded in aortic stenosis (Fig. 6), whereas in severe aortic insufficiency both curves are grossly distorted, with disproportionate prolongation of disappearance time.

three subgroups ($p < 0.05$). The mean T_B and T_M were more prolonged in patients with aortic stenosis than in those with mitral stenosis, although there was no significant difference in T_D and 1/S between these two subgroups.

DISCUSSION

The values of "central" blood volume in patients with mitral and/or aortic valvular disease determined by the present technique agree closely with those reported by other workers.[8-11]

Estimates of pulmonary blood volume in patients with valvular heart disease have been reported recently by Dexter[12] and Milnor[13] and their respective associates. Both groups of investigators demonstrated that the pulmonary blood volume in their patients is much smaller, and the left heart–arterial volume larger than was previously supposed. The present study points out that the mean PA to LA volume does not vary significantly in patients with different types of valvular lesions. Our values which include left atrial blood volume are of the same order as, or slightly greater than, those reported by Dexter and Milnor and their co-workers. The mean LV to FA volume is usually greater in patients with predominant aortic valvular lesions than in those with predominant mitral valvular lesions.

A normal PA curve was not observed in any patient who had a subnormal forward cardiac index or increased "central" blood volume. The PA curve was grossly abnormal in all patients with predominant valvular insufficiency, except for 2 who had a mild degree of mitral insufficiency. These findings were in accordance with the observations reported by other workers.[6,14] Recently, Rowe and Hoffman[15] demonstrated that in a circulatory model with "valvular" insufficiency the nature of the regurgitant jet and of the proximal chamber which it enters may play an important role in determining the contour and time components of the dilution curve.

Study of dilution curves recorded after the injection of indicator into the left atrium or the left ventricle has yielded valuable information about the nature and severity of valvular lesions on the left side of the heart.[14,16-19] The results of the present study show that comparison of PA and LV curves in a given patient may be of special value in the differential diagnosis of mitral or aortic valvular lesions.

In patients with uncomplicated mitral stenosis of moderate severity, although the contour of the PA curves is distorted with prolongation of two or more time components, the contour of the LV curve is similar to that of the PA curve obtained in normal subjects. In patients with predominant mitral stenosis associated with cardiac decompensation or other valvular lesions the LV curve may show prolongation of most of the time components, in comparison with that obtained in uncomplicated cases. This change may be due to a markedly decreased forward cardiac index or increased left ventricular "residual" volume, or both.

In the presence of predominant mitral insufficiency the PA curves are almost always abnormal, whereas the contour of the LV curves is largely determined by the severity of insufficiency. If the regurgitation is small, the LV curve appears

normal. If there is moderately severe or severe insufficiency, there is prolongation of T_A, T_M, T_D, and 1/S in the LV curve, and the peak of systemic recirculation is usually not identifiable. These changes are attributable to repeated dilution of the indicator by the abnormal backflow through the incompetent mitral valve and to increased left ventricular volume.

In patients with predominant aortic valvular disease, since injections of indicator are made at the sites proximal to the lesion, both PA and LV curves are similar in contour, in that there is prolongation of all time components. If there is marked aortic insufficiency, the dilution curves are further characterized by a broad top and a disproportionate prolongation of disappearance time.

The values of T_D and 1/S of the LV curves may serve as a means of differentiating between predominant mitral valvular disease and aortic stenosis, on the one hand, and predominant aortic insufficiency, on the other. The disproportionate prolongation of T_D and 1/S of the LV curves in patients with predominant aortic insufficiency cannot be entirely explained on the basis of either change in forward cardiac index or LV to FA volume. It would be reasonable to assume that the presence of regurgitant flow with delayed clearance of the indicator from an increased "residual" volume in the left ventricle is probably the main factor. These findings are analogous to the observations made by Abelmann and co-workers,[19] that is, after the injection of indicator into the left atrium the disappearance time and reciprocal of downslope in the dilution curve are two of the most sensitive parameters to differentiate predominant mitral insufficiency from predominant mitral stenosis.

SUMMARY AND CONCLUSIONS

1. Indicator dilution curves were recorded from the femoral artery after the injection of either I^{131} HSA and/or Cardiogreen into (a) the pulmonary artery in 7 healthy subjects and in a series of 89 patients with various types of valvular heart disease, and (b) the left ventricle in 36 patients with valvular heart disease.

2. In general, the total blood volume was greater in patients with valvular insufficiency than in those with valvular stenosis. The mean "central" blood volume in patients with mitral insufficiency or aortic valvular lesions was significantly greater than that in healthy subjects. In all subgroups, the mean ratio of the "central" blood volume to the total blood volume was remarkably constant, varying between 23.4 and 26 per cent. Two successive determinations of the "central" blood volume showed a variation of less than 100 ml./M.^{2} in 22 of 24 patients.

3. The mean LV to FA volume in patients with predominant aortic valvular lesions was significantly greater than that in those with predominant mitral stenosis or mitral insufficiency.

4. The contour and the time-concentration components of the PA curves in 7 healthy subjects were described. The PA curves were abnormal in all but 8 patients with valvular heart disease.

5. The LV curves in patients with "pure" mitral stenosis or mild mitral insufficiency resemble the PA curves in healthy subjects. In patients with mod-

erately severe or severe mitral insufficiency the disappearance time of the LV curves is usually prolonged, and the peak of systemic recirculation is not clearly identifiable.

6. In patients with aortic valvular lesions, both PA and LV curves were abnormal and similar in contour, with prolongation of all time components. The value of disappearance time in the LV curves was 25 seconds or less in all patients with mitral valvular disease or aortic stenosis. It exceeded 25 seconds in more than one half of the patients with aortic insufficiency. The value of the reciprocal of downslope was less than 9 in all patients with mitral valvular disease and in 8 of 10 patients with aortic stenosis, but it exceeded 9 in more than two thirds of the patients with predominant aortic insufficiency.

7. Comparison of the PA and LV curves may give information about the nature and severity of the left-sided valvular lesions as well as the size of the compartments comprising the "central" blood volume.

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Gitalin Studies

David R. Fleisher, B.S., and Leonard M. Linde, M.D., Los Angeles, Calif.

The amorphous derivative of *Digitalis purpurea* known as "gitalin" or "verodigen" was described in 1919.[1] It has been widely used in Europe as a cardiotonic agent,[2,3] even though its clinical superiority and existence as a distinct chemical and pharmacologic entity have been in dispute.[4-9]

Little attention was paid to this substance in the United States until 1950, when Batterman published evidence to show that the therapeutic ratio (therapeutic dose to toxic dose, as defined by Batterman) of this digitalis preparation is 30 to 40 per cent, whereas the therapeutic ratio of all other cardiac glycosides is about 60 per cent.[10-13] The allegedly more favorable therapeutic ratio of gitalin would make it the digitalis preparation of choice since its use would decrease the frequency and danger of digitalis intoxication. In addition, it would be useful in patients with decompensation which had become refractory to other forms of digitalis.

Batterman's findings evoked considerable clinical and pharmacologic investigation of gitalin.[14-22] Conclusions ranged from complete agreement to complete disagreement with Batterman. Of special importance were the basic pharmacologic experiments with gitalin made by Gruhzit and Farah in 1953.[23] They attempted to determine the therapeutic ratio of gitalin by using the dog heart-lung preparation. These experiments showed no greater margin of safety with gitalin. The gitalin used by Gruhzit and Farah was ". . . prepared by diluting alcoholic stock solutions of the glycosides to the desired concentration with physiologic saline." This is of interest in view of work done by a group of German chemists, in 1955-56, which is of great importance to research on cardiac glycosides, gitalin in particular.

In April, 1956, E. Haack and co-workers[24] published the first successful chemical analysis of "the gitalin fraction." They found, in addition to digitoxin and gitoxin, large amounts of a heretofore unknown cardiac glycoside called *gitaloxin*. This compound is identical with gitoxin, except that the hydroxyl on carbon 15 of gitoxin is esterified with formic acid.

Thus, gitaloxin is 15-formyl-gitoxin. A smaller amount of a second previously unknown formyl ester, *formyl-strospeside*, was also discovered. Table I enumer-

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ates the individual constituents of "the gitalin fraction." The major portion consists of about equal parts of digitoxin, gitoxin, and gitaloxin; the rest consists of formyl-strospeside, other glycosides and inactive aglycones, and noncardiotonic "companion substances."

What is the significance of these newly discovered cardiac glycosides? Comparison of the chemical formulas (Fig. 1) of the newly discovered formyl esters with their long-known unesterified analogs is not so impressive as comparison of their pharmacologic properties. Achelis and Kroneberg[25] have shown that formylation of the hydroxyl on carbon 15 dramatically increases potency. Their study of prepared mixtures of the gitalin-fraction glycosides showed that *gitaloxin*, although present in about the same concentration as digitoxin, contributed 2½ times as much glycosidal activity. Moreover, Haack and co-workers,[24] comparing many different samples of *Digitalis purpurea* from different geographical sources and botanic strains, showed that the efficacy of each sample ". . . correlates neither with the digitoxin, nor with the gitoxin content, but only with the gitaloxin content, indicating that the latter is the determining factor in the guinea pig assay." Regarding formyl-strospeside, Haack and co-workers[24] state that " . . . just as with the conversion of gitoxin to gitaloxin, a considerable increase in activity results when strospeside is esterified with formic acid." Also, earlier investigators were correct in their belief in the existence of a special gitalin fraction which differed considerably from digitoxin and gitoxin, for the characteristic properties of verodigen are due to the hitherto unknown glycosides, gitaloxin and formyl-strospeside."

One further revelation of Haack and co-workers perhaps provides the key to eventual settlement of the controversy surrounding gitalin: *Potent as the formyl esters are, they nevertheless undergo spontaneous hydrolysis to the less potent gitoxin and strospeside under a variety of circumstances.* Aqueous, alcoholic, or alkaline media, heat, time, the alumina used in chromatography columns, and many other agents will promote the hydrolytic degradation of these ester bonds. (See Fig. 1 for a schematic presentation of the structural relationships of *Digitalis*

TABLE I. THE CONSTITUENTS OF AMORPHOUS GITALIN*

Digitoxin, Gitoxin, Gitaloxin	40 to 50%
Strospeside	4 to 6%
Formyl-Strospeside	2 to 3%
Odoroside-H, Aglycones	1 to 2%
"Companion Substances"	39 to 53%
Total	100%

*From Haack, et al.[24]

purpurea glycosides.) Although gitaloxin is practically completely stable in absolutely dry leaves, even traces of moisture in apparently dry preparations will produce a gradual increase in gitoxin at the expense of gitaloxin, and strospeside at the expense of formyl-strospeside. Alcoholic solutions will contain little or no gitaloxin after prolonged standing, although the formic-ester glycosides are far more stable in tablet form.

Recently, Linde and co-workers[26] attempted a pediatric clinical trial of Gitaligin Drops,* a preparation of amorphous gitalin in aqueous-alcoholic solution. Their patients developed ECG signs of toxicity which persisted longer than anticipated, a response more characteristic of digitoxin than gitalin.

This lability of two of the constituents of gitalin prevented their discovery for 45 years, obscured answers to questions of digitalis deterioration,[27,28] and caused Stoll[6] and many other investigators to doubt the existence of glycosides other than digitoxin and gitoxin in "the gitalin fraction."

Examination of the American literature of the past decade on gitalin reveals that the various investigators did not consider the chemical nature of the preparation used. The gitalin was used in dry, aqueous, and tincture form. Whereas they all assumed that one drug was under investigation, they in fact studied mixtures whose constituents and potencies must have varied considerably! The critically important pharmacologic studies of Gruhzit and Farah,[23] which showed no evidence for a special therapeutic ratio for gitalin, were done with gitalin ". . . prepared by diluting *alcoholic stock solutions*† of the glycosides to their desired concentrations with physiological saline."

Another important discovery of the German investigators concerns gitalin's noncardioactive, organic molecules in which the cardiotonic glycosides are dispersed. These leaf materials comprise 40 to 50 per cent of the gitalin fraction.[24] Although not biologically active, they are far more than inert filler of "ballast substances" as was once thought. Haack explains the importance of the inert leaf substances in gitalin in the following way: Purified glycosides are more or less poorly soluble. In gitalin, the hydrophobic cardiac glycoside molecules are surrounded by hydrophilic organic molecules which (1) permit the glycoside molecules to enter into solution more readily, and (2) keep the size of the molecular aggregates of the glycosides small, thereby making the glycosides more diffusible once dissolved. Kroetz and Foerster[29] compared the potency of gitoxin when given in the pure form and when mixed with the inert leaf substances. They found that 4.8 mg. of gitoxin plus "companion substances" was equivalent to 16.0 mg. of pure gitoxin. The prevailing opinion has been that gitoxin is a glycoside of little clinical importance, because in the pure state it is insoluble and therefore not absorbed. Yet, the afore-mentioned evidence indicates that gitoxin, as present in gitalin, significantly contributes to the cardiotonic action of this drug.

Enlightened studies of gitalin and its individual glycosides have recently been reported by Kroetz and Foerster,[29] Cloetens and co-workers,[30] and Hoch-

*White Laboratories, Inc., Kenilworth, N. J.
†Italics added.

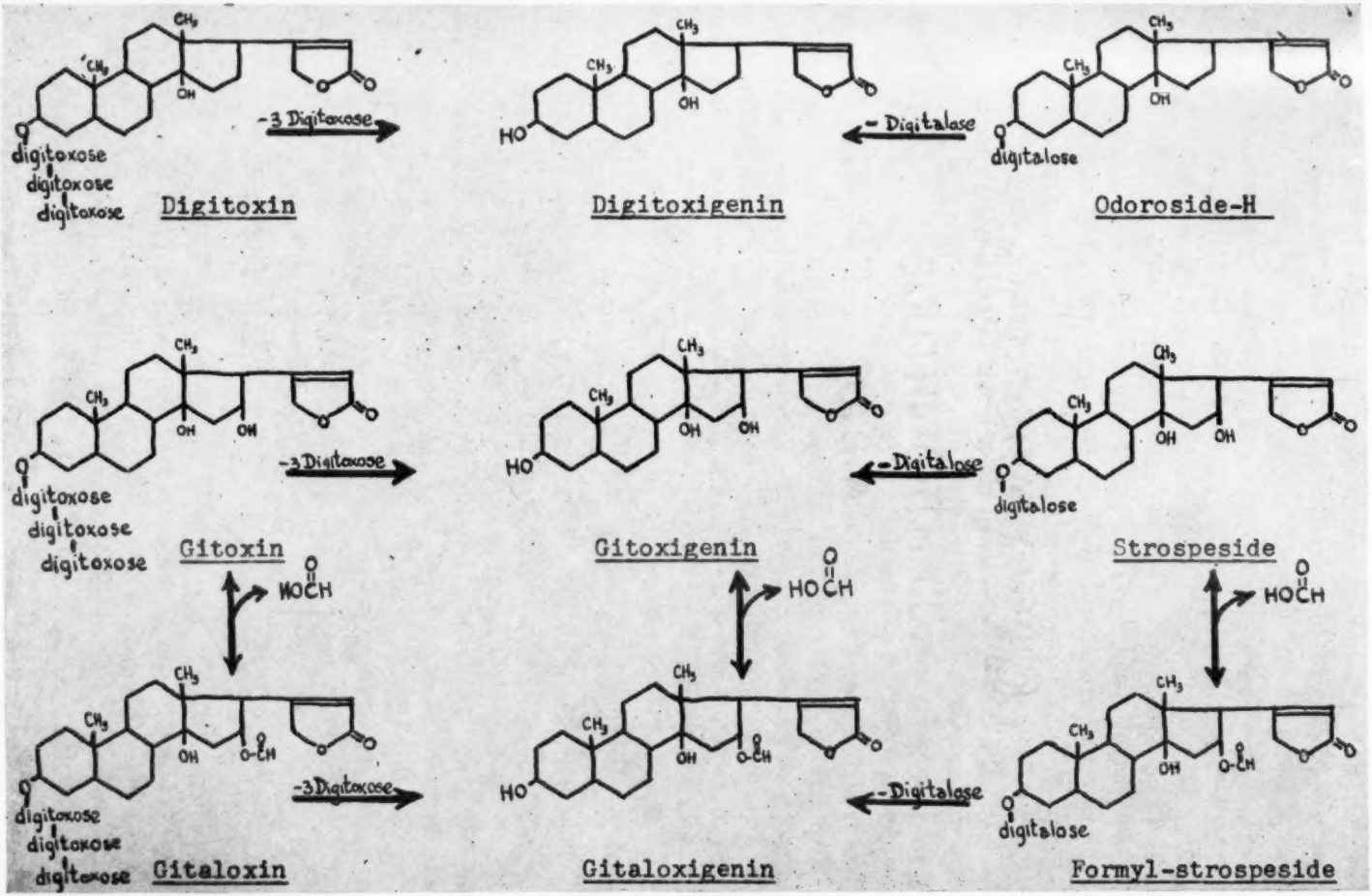

Fig. 1.—The structural relationships of the *Digitalis purpurea* glycosides (From Stoll[6] and Haack, et al.[24]). *A*, Active glycosides present in larger proportions. *B*, Inactive aglycones. *C*, Active glycosides present in small proportions.

rein.[31] All of the patients of Kroetz's study were hospitalized and nonambulatory, all were in cardiac decompensation due either to essential hypertension or to chronic rheumatic heart disease, and all had suffered from chronic moist cardiac insufficiency which began between the ages of 45 and 75 years. None of the patients were given cardiac drugs 3 to 7 days prior to entrance into the study; those who were on adjuvant therapeutic regimens (e.g., low-sodium diet, strict bed rest, etc.) were stabilized in the status of their decompensation before the start of the trial. All of the patients had auricular fibrillation with ventricular tachyarrhythmia. Quantitation of therapeutic effect was made on the basis of ventricular slowing. Data regarding each patient's dosages, changes in body weight, and fluid balance were graphically presented in detail. Kroetz and Foerster present valuable information concerning the absorption and time course within the body of gitalin's constituent glycosides, as well as the effect of "companion substances" on the clinical activity of these drugs. Their findings are compatible (although not always in strict agreement) with those reported in the papers of Haack and co-workers and Achelis and Kroneberg. None of these German papers deals specifically with the question of therapeutic ratio.

Five years have passed since the discovery of gitaloxin and formyl-strospeside. The questions of toxicity and therapeutic range still remain unsettled. At present, a new series of clinical and pharmacologic trials is needed, with awareness of the chemical properties of the constituents of gitalin, using preparations of known standardized composition and stability, with statistically valid numbers of subjects and controls.

SUMMARY

(1) The literature on gitalin up to 1950 is briefly mentioned. Up to that time, the usefulness and existence of gitalin as a chemical entity was widely doubted. (2) In the early nineteen-fifties, Batterman stated that gitalin is inherently less toxic than other digitalis preparations. (3) Batterman's findings provoked many clinical and pharmacologic investigations by many workers whose results ranged from complete agreement to complete disagreement with his statements. All of these investigations had in common the fact that none of them were based on a clear understanding of the chemical nature of gitalin. (4) The chemistry of gitalin was brought to light in 1956, by Haack and co-workers, who discovered that it was a glycosidal mixture which contained two new glycosides, *gitaloxin* and *formyl-strospeside*. (5) Thus, previous researchers studied and reported on a drug without knowledge of the existence of two very potent but extremely labile constituents. Re-evaluation of their conflicting results and new investigations are indicated, modified according to the discoveries of Haack and others. (6) Biologically inactive leaf substances which make up about half of the "gitalin fraction" have been found to increase the solubility and diffusibility of cardiac glycosides. Gitoxin, long thought to be useless because of its poor absorption, instead plays an important cardiotonic role when in the presence of these nonactive "companion substances." (7) Standards are suggested for future clinical trials of cardiac glycosides.

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Acetylcholine in Differential Diagnosis and Treatment of Paroxysmal Tachycardia

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INTRODUCTION

The differential diagnosis of paroxysmal tachycardia is sometimes difficult to establish with certainty, which leads to greater uncertainty regarding treatment. It is especially important to differentiate between ventricular tachycardia and auricular flutter with bundle branch block. Procaine amide has been used for this purpose.[1] Another useful way in which this differentiation can sometimes be made, occasionally with termination of the episode, is to alter auriculoventricular conduction by vagal stimulation, employing carotid sinus massage or eyeball pressure. Vagomimetic drugs, such as methacholine and neostigmine, are effective, but produce such prolonged and severe side effects that they are less than ideal agents.

It appeared to us that the ideal agent for brief vagomimetic effect of graded intensity should be acetylcholine administered intravenously. It had previously been well demonstrated in normal subjects that the rapid intravenous injection of 15 to 30 mg. of acetylcholine hydrochloride produced satisfactory stimulation. Carmichael and Fraser[2] described the usual response very well: "A few seconds after injection the heart rate would slow abruptly and simultaneously the subject experienced a sense of obstructed breathing, causing him to cough, or a feeling of constriction in the chest and other minor sensations, such as burning in the throat. Increased rate and depth of breathing was often noticed. The slowing of the heart, the sensation in the throat, and the desire to cough lasted only a few seconds and were followed by a rise of heart rate to a level greater than before injection, by the appearance of a flush over the face and neck, by a sensation of heat throughout the face, trunk and limbs, and in some subjects by palpitation. This second phase passed off gradually and the whole reaction was over in a half to one minute."

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These observations were confirmed and extended by Segers and associates,[3] who also used intravenous injections in normal subjects. They reviewed a number of reports on the physiologic and therapeutic effects of acetylcholine injected subcutaneously and intramuscularly and concluded that those routes were not satisfactory. This was also in agreement with the results of Carmichael and Fraser.[2] They then successfully treated 41 episodes of supraventricular tachycardia in 6 patients with graded doses of from 20 to 100 mg. given intravenously at 3- or 4-minute intervals.[4] The effective dose varied considerably from patient to patient, but was relatively constant in any given patient. Termination of the tachycardias within 30 seconds after injection was followed by transient bradycardia, frequent auricular and ventricular ectopic beats, and regular sinus rhythm within 1 to 2 minutes. If the paroxysm recurred, it could again readily be terminated by a repeated injection of acetylcholine. The side effects in their cases lasted no more than a minute, and occurred in 20 per cent of the episodes treated.

Only one additional article[5] was found in which acetylcholine was reported to have been used intravenously for paroxysmal tachycardia; the drug was successful in 5 cases but details were not given. In both papers on therapy, acetylcholine was regarded as the agent of choice for paroxysmal (supraventricular) tachycardia, particularly in comparison with Mecholyl, which gave more frequent, severe, and longer lasting side effects. It was therefore difficult for us to understand why acetylcholine has subsequently been used very little and Mecholyl (and Prostigmin) have been employed extensively.

This report presents data which further demonstrates the diagnostic and therapeutic value of acetylcholine in cases of paroxysmal tachycardias.

METHODS

When a patient was discovered to have rapid heart action, the tachycardia team was notified. An electrocardiogram was recorded during which carotid sinus pressure was applied. The lead best demonstrating auricular activity was chosen for monitoring. If auricular complexes were not discerned, a lead in the area of Lead V_1 was used. An intravenous infusion of 5 per cent glucose was started in order to facilitate rapid administration of multiple doses of acetylcholine. This technique offered the additional advantage of avoiding multiple venipunctures. Perhaps the greatest merit was the avoidance of withdrawal of blood into the syringe; since cholinesterase activity of blood is rapid, a factor possibly contributing to variation in response was eliminated. Each individual dose of 10 to 20 mg. of acetylcholine was given in a volume of 1.0 ml., dissolved in saline injected into the tube of the 5 per cent glucose infusion. Increasing doses were administered, beginning with 10 to 20 mg. The administration of the dose and the patients' side reactions were timed with the continuously recording electrocardiograph. Increments of the drug were administered at 3- to 5-minute intervals, between which blood pressure was recorded. The largest single dose was 220 mg.

RESULTS

A. *Treatment of Paroxysms.*—

1. *Supraventricular tachycardia:* The dosage and results of treatment of 11 patients with supraventricular tachycardia are summarized in Table I. Of 9 patients (Patients 1 to 9) with paroxysmal nodal tachycardia, graded doses

TABLE I. DATA ON TREATMENT OF TACHYCARDIA WITH ACETYLCHOLINE

PATIENT, SEX, AGE	CLINICAL DIAGNOSES	ECG DIAGNOSES*	PRETREATMENT CARDIAC RATE		DOSES OF ACETYCHOLINE (MG.)		REMARKS
			AURICULAR	VENTRICULAR	WITHOUT ECG EFFECT	WITH ECG EFFECTS	
			Supraventricular Tachycardia				
1. F, 26	Rheumatic heart disease	PNT, 1:1 N:A	255	255	10, 20	40: sinus rhythm	Transient retching
2. F, 46	Cirrhosis	PNT, 1:1 N:A	125	125	25	40, 60, and 80: transient sinus rhythm	Rate previously slowed from 170 to 125 by procaine amide
3. M, 57	Arteriosclerotic heart disease	PNT, 1:1 N:A	180	180	20, 30, 60, 80, 100		
4. F, 61	Arteriosclerotic heart disease	PNT, 1:1 N:A	185	185	20, 40	50: transient slowing 70: sinus rhythm	
5. F, 70	Arteriosclerotic heart disease	PNT, 1:1 N:A	155	155		20: sinus rhythm	
6. F, 61	Bronchogenic carcinoma	PNT, 1:1 N:A	245	245	15, 20, 40	40: sinus rhythm after vomiting	Vomiting may have terminated tachycardia
7. M, 58	Arteriosclerotic heart disease	PNT, 1:1 N:A	155	155	20, 40, 60	80: sinus rhythm	
8. F, 63	Diabetes mellitus	PNT, 1:1 N:A	205	205	20	40: sinus rhythm	
9. F, 60	Lobar pneumonia	PNT, 1:1 N:A	190	190	25	50: sinus rhythm	
10. M, 54	Arteriosclerotic heart disease	PAT, 1:1 A:V	200	200	25	50: sinus rhythm	Transient aberrant ventricular conduction
11. M, 47	Bronchopneumonia	PAT, 1:1 A:V	?	180	20, 40	60, 70, and 90: transient 2:1 A:V block; Wenckebach phenomena, and aberrant ventricular conduction	Initial diagnosis of PNT was excluded by auricular complexes during 2:1 A:V block
			Auricular Flutter				
12. F, 53	Carcinoma of cervix	Flutter, 2:1 A:V	360	180	20	40: transient 3:1 A:V conduction 60: transient 4:1 A:V conduction 80: sinus rhythm	Flutter with 2:1 A:V conduction Recurred after 24 hours
13. F, 38	Rheumatic heart disease	Flutter, 2:1 A:V	360	180	20, 40	60: transient 3:1 and 4:1 A:V conduction 80: 3 second A:V block	

14. M, 55	Arteriosclerotic heart disease	Flutter, 2:1 A:V	330	165	25, 50, 75, 100	125: transient 3:2 A:V conduction	
15. F, 70	Arteriosclerotic heart disease	Flutter, 2:1 A:V	290	145	20	40: 2 second A:V block	
16. F, 43	Rheumatic heart disease	Flutter, 2:1 A:V	330	165	20	40: transient 3:1 A:V aberrant ventricular conduction 60: transient A:V block	Transient substernal pressure
17. M, 49	Possible myocardial infarction	Flutter, varying A:V	480	130±	20	20, 40 and 60: slight transient decrease in A:V conduction	
18. M, 68	Arteriosclerotic heart disease	Flutter, varying A:V	310	145±	20, 40	80: transient 4:1 A:V conduction 120: transient 3:1 and 4:1 A:V conduction with occasional Ashman phenomenon	
19. F, 80	Arteriosclerotic heart disease	Flutter, varying A:V	300	180±	20	40 and 60: transient A:V block	Flutter waves revealed during A:V block
20. M, 46	Rheumatic heart disease	Flutter, 2:1 A:V, RBBB	400	200	10	30, 50, 70, 100 and 120: transient 4:1 A:V conduction	Flutter waves revealed during A:V block
21. M, 69	Arteriosclerotic heart disease	Flutter, 2:1 A:V, LBBB	280	140	20, 40	50, 80, 100, 120 and 150: transient 4:1 to 6:1 A:V conduction	Flutter waves revealed during A:V block
22. F, 87	Arteriosclerotic heart disease; hemiplegia	Flutter, 2:1 A:V, RBBB	320	160		20, 40, 60, 70, and 90: transient 3:1 to 4:1 A:V conduction	Flutter waves revealed during A:V block
23. M, 72	Arteriosclerotic heart disease	Flutter, 2:1 A:V, RBBB	320	160	30, 50, 80, 140, 180, 220		Flutter waves revealed during A:V block induced by procaine amide
24. M, 57	Arteriosclerotic heart disease	Flutter, 2:1 A:V, RBBB	400	200		20: transient 4:1 A:V conduction 40 and 60: transient A:V block, aberrant ventricular conduction, and sinus rhythm	Flutter recurred after 30 seconds both times
25. F, 64	Arteriosclerotic heart disease	Flutter, varying A:V, RBBB	360	220±	25	50 and 80: transient A:V block	Flutter waves revealed during A:V block
					Ventricular Tachycardia		
26. F, 58	Coronary artery disease	PVT, sinus P waves	90	215	20, 40, 60, 80, 100, 120, 140, 160, 200		
27. M, 37	Idiopathic cardiac hypertrophy	PVT, 2:1 V:A	105	210	60, 80, 100, 140		

******PNT*. **Paroxysmal nodal tachycardia.** *PAT*. **Paroxysmal auricular tachycardia.** *PVT*. **Paroxysmal ventricular tachycardia.** *N:A*. **Nodal-auricular (retrograde) conduction ratio.** *V:A*. **Ventriculoauricular (retrograde) conduction ratio.** *A:V*. **Atrioventricular conduction ratio.** *RBBB*. **Right bundle branch system block.** *LBBB*. **Left bundle branch system block.**

of acetylcholine, from 20 to 80 mg. administered intravenously, terminated the episodes in 7. A typical result is shown in Fig. 1. In Patient 2 the tachycardia recurred within 1 minute after each of three terminations of the tachycardia. In Patient 6, injection of the drug was followed by vomiting, then termination of the tachycardia. Acetylcholine was without effect in Patient 3.

Of 2 patients with paroxysmal auricular tachycardia, acetylcholine terminated the tachycardia in one (Patient 10) and failed in the other (Patient 11). In all, 8 of 11 patients were successfully treated with acetylcholine, without recurrence.

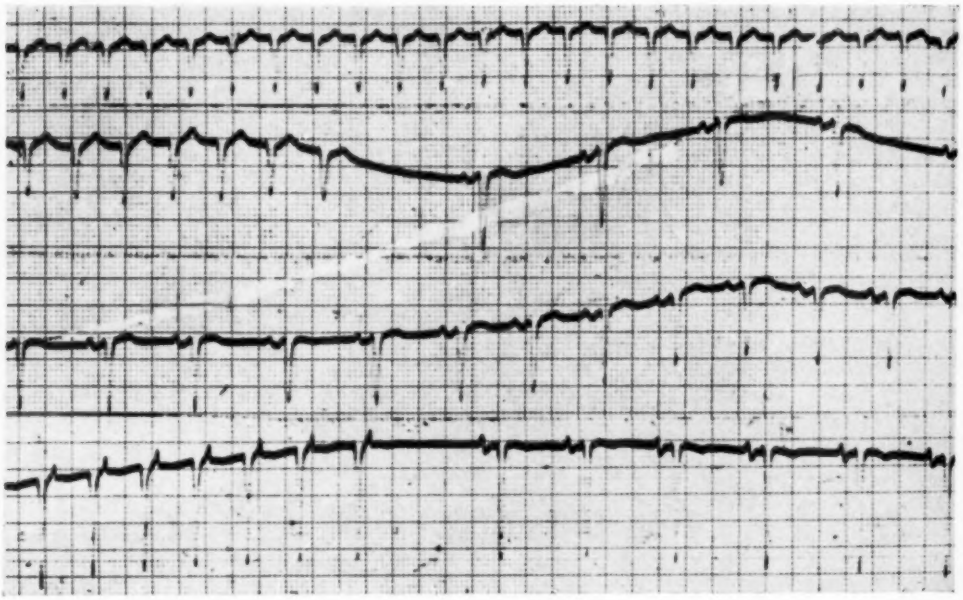

Fig. 1.—Continuous strip of Lead V_1 in Patient 7. After 80 mg. of acetylcholine the paroxysmal nodal tachycardia terminates, with recurrence for only 7 beats in the last strip.

The severity of side effects determined the number and size of doses administered. The side effects as described above were experienced at one or more of the dosages administered in 7 of the 11 patients, but were easily tolerated because of their short duration. Retching occurred for 30 to 60 seconds in two patients and, this, rather than the drug itself, may have been responsible for termination of the tachycardia in one of them (Patient 6). Transient aberrant ventricular conduction occurred in only one patient (Patient 10).

2. *Auricular flutter:* The data on treatment of 14 patients with auricular flutter and rapid ventricular rate are summarized in Table I. These included 5 patients with 2:1 A-V conduction (Patients 12 to 16), 3 with varying A-V conduction (Patients 17 to 19), 5 with 2:1 A-V conduction and bundle branch block (Patients 20 to 24), and 1 with varying A-V conduction and bundle branch block (Patient 25). Acetylcholine terminated the auricular flutter in only 2 patients, and in both there was recurrence. In Patient 24 the arrhythmia recurred in 30 seconds, and in Patient 12 in 24 hours.

Doses of acetylcholine were increased to levels which caused side reactions in 13 of the 14 patients. Transient aberrant ventricular conduction occurred in 3 patients (Patients 16, 18, and 24), accompanied by momentary chest pain and pressure sensation in one (Patient 16).

3. *Ventricular tachycardia:* In 2 patients with typical paroxysmal ventricular tachycardia, one with superimposed sinus P waves (Patient 26), the other with retrograde P waves with 2:1 V-A conduction (Patient 27), acetylcholine in doses up to 200 mg. was without electrocardiographic effect or significant side reactions. In both cases the electrocardiographic diagnoses were confirmed upon termination with procaine amide.

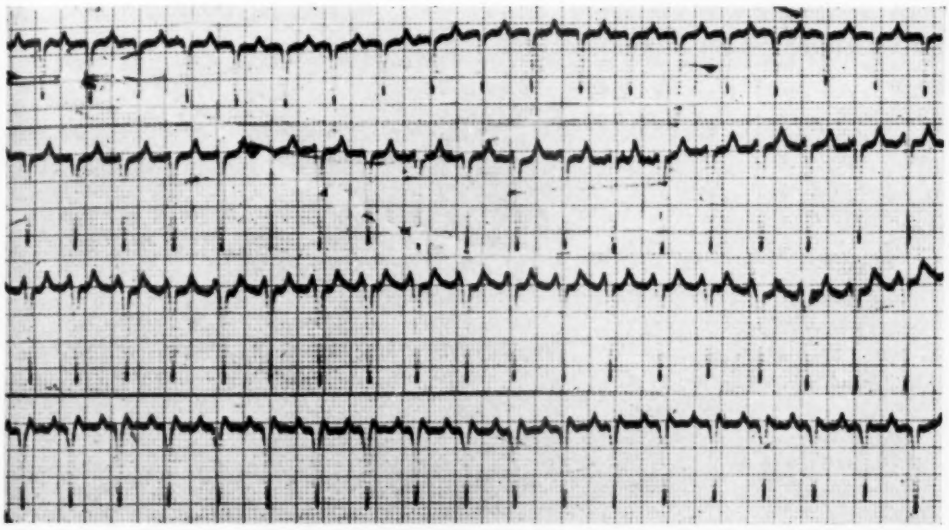

Fig. 2.—Continuous strip of Lead V_1 in Patient 16. Initially the appearance is that of auricular or nodal tachycardia. After 60 mg. of acetylcholine there was variation in A-V conduction which permitted identification of the previously hidden alternate F waves. This alternate F wave was at first hidden in the QRS; in the third strip it simulates an R deflection, and in the last strip it simulates R′. In the last two strips it is clear that the F-F interval is constant at a rate of 330 with 2:1 A-V conduction.

B. *Differential Diagnostic Value.—*

1. *Differentiation of known supraventricular tachycardias (QRS complexes of normal duration)*: In 5 patients (Patients 12 to 16) in whom auricular flutter was suspected, acetylcholine caused transient A-V block, which clearly revealed the auricular flutter waves and confirmed the suspected diagnosis of flutter with A-V conduction. In 3 patients (Patients 17 to 19) who had auricular flutter with rapid ventricular response but with varying A-V conduction the auricular flutter waves could be delineated before acetylcholine was administered; flutter waves were clearly revealed during the induced transient A-V block. In Patient 11 the transient A-V block led to the diagnosis of auricular tachycardia with 1:1 A-V conduction rather than the nodal tachycardia with 1:1 retrograde conduction which had been diagnosed previously.

2. *Differentiation of suspected ventricular tachycardias (QRS complexes of prolonged duration):* Acetylcholine was administered to 6 patients with auricular

flutter and bundle branch block simulating ventricular tachycardia (Patients 20 to 24 who had 2:1 A-V conduction, and Patient 25 with varying A-V conduction). In 4 patients (Patients 20, 21, 22, and 25), the transient A-V block allowed unequivocal measurement of flutter waves between ventricular complexes, clearly indicating the true mechanism. In Patient 24, transient conversion to sinus rhythm with persistence of the bundle branch block established the diagnosis of auricular flutter (Fig. 4). In Patient 23 the diagnosis of ventricular tachycardia was made because no A-V block occurred with acetylcholine. Treatment with procaine amide induced transient A-V block, which revealed flutter waves and established the true diagnosis of auricular flutter with 2:1 A-V conduction with bundle branch block.

In 2 patients with confirmed diagnoses of ventricular tachycardia, no alteration was induced by administration of acetylcholine.

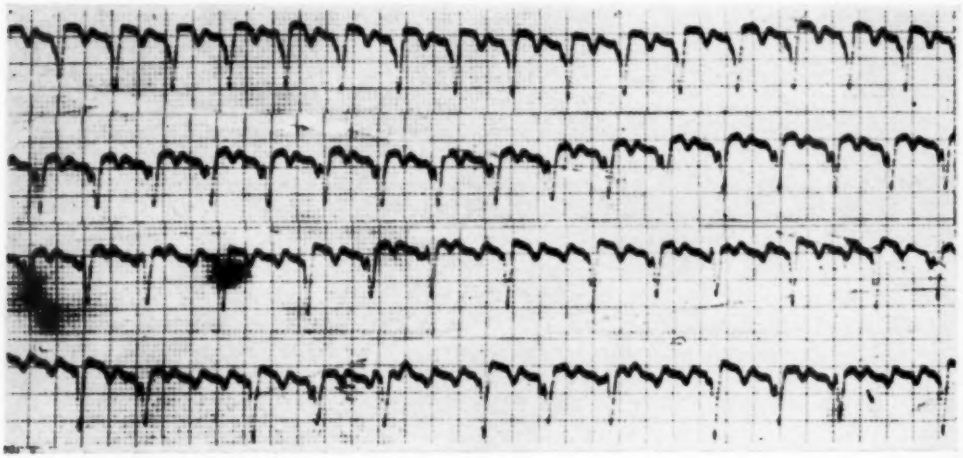

Fig. 3.—Continuous strip of Lead V_1 in Patient 21. After 50 mg. of acetylcholine there was varying A-V block which permitted recognition of F waves. Ventricular tachycardia is excluded by persistence of broad QRS complexes of the same configuration.

DISCUSSION

The results require discussion in two categories, therapeutic and diagnostic, because in those cases in which conversion was not achieved important diagnostic information was acquired which often led to successful therapy with other agents.

A. *Termination of Paroxysms of Tachycardia.*—Supraventricular tachycardia was successfully treated without recurrence in 8 of 11 patients. This was accompanied by insignificant or easily tolerated side effects and indicates that acetylcholine administered intravenously should be considered a valuable agent in the treatment of this arrhythmia. It has the distinct advantage over other parasympathomimetic drugs of producing effects which are of very short duration, thus allowing repeated dosage without use of atropine. This permits precise determination of the dose required to terminate the tachycardia without persistence of side effects of either the therapeutic drug (e.g., Mecholyl or Prostigmin) or its antagonist (atropine).

Although doses of acetylcholine produced significant side reactions in 14 patients with auricular flutter with rapid ventricular response, the tachycardia was terminated in only 2, with recurrence of the arrhythmia in both. It is apparent, therefore, that acetylcholine is of no value as a therapeutic agent in auricular flutter with rapid ventricular response.

In 2 patients with paroxysmal ventricular tachycardia, acetylcholine was without effect.

B. *Diagnostic Value.*—In tachycardias of known supraventricular origin (QRS of normal duration), the differential diagnostic value of acetylcholine lies in its ability to cause a transient block of A-V conduction, revealing the pattern of auricular activity previously obscured by overlying QRS complexes. The most common problem of this nature is auricular flutter with regular 2:1 A-V conduction in which alternate F waves are lost within the QRS complexes. In cases of paroxysmal rapid heart action due to auricular flutter, acetylcholine is very effective in revealing the mechanism.

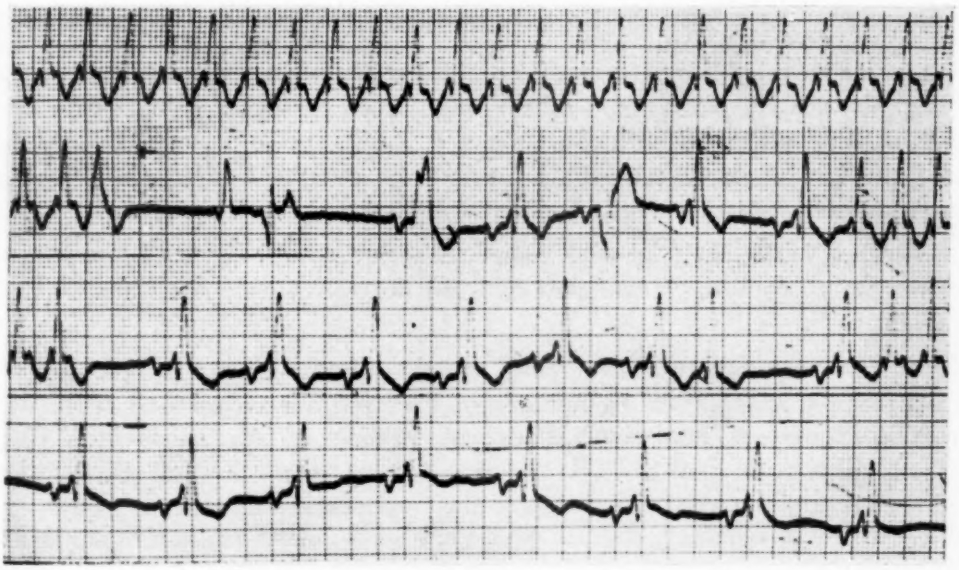

Fig. 4.—Continuous strip of Lead V_1 in Patient 24. The initial configuration resembles ventricular tachycardia. Previously, 20 mg. of acetylcholine induced transient 4:1 A-V conduction, revealing F waves. After 60 mg. there was transient aberrant ventricular conduction followed by a few conducted sinus beats, 6 beats of the original rhythm and configuration, then sinus rhythm with bundle branch block.

In any electrocardiogram which shows a rapid rate and wide QRS complexes it is imperative to distinguish ventricular tachycardia from a supraventricular mechanism with aberrant conduction or bundle branch block. This differentiation may be of life-saving importance because of the different therapeutic implications.

The differentiation of auricular tachycardia, nodal tachycardia, and auricular flutter with ventricular complexes of normal duration is not of crucial importance because they all may be properly treated with the same medications.

Acetylcholine is of great value in effecting this differential diagnosis by producing a transient A-V block which reveals the underlying auricular activity. For example, in one instance of flutter and right bundle branch block, transient conversion to sinus rhythm with preservation of the right bundle branch block pattern proved the auricular origin of the tachycardia.

C. *Factors Determining Dosage of Acetylcholine.*—The arm-to-lung circulation time is long enough for inactivation of significant amounts of acetylcholine. The amount of drug inactivated will depend on the enzymatic activity of the blood, which we did not estimate, and the circulation time. In 20 patients the circulation time was estimated, using respiratory "gasp" as an end point, and comparison was made with the dose required. A slight but statistically insignificant correlation existed ($r = 0.37$, $P = 0.10$). If an electrocardiographic end point were used and blood cholinesterase activity determined, it is possible that a better understanding could be obtained of the wide variation in dose required.

SUMMARY

1. Increasing doses of acetylcholine hydrochloride were given intravenously to 27 patients with paroxysmal tachycardia. Each dose was given in a volume of 1.0 ml. injected rapidly into the tube of an infusion of 5 per cent glucose, providing uniform "bolus effect." This method also avoided hydrolysis by cholinesterases incident to barbotage.

2. In 8 of 11 patients with paroxysmal supraventricular tachycardia the episodes were promptly terminated and did not recur. Side reactions were mild or absent.

3. Fourteen patients with paroxysmal auricular flutter with rapid ventricular rate were treated. In none were the episodes terminated without recurrence. However, in all cases there were transitory alterations in A-V conduction which sometimes clarified the diagnosis of the mechanism. In 5 patients with flutter and bundle branch block the important possibility of ventricular tachycardia was excluded when the F waves were revealed during the momentary A-V block.

CONCLUSIONS

1. Acetylcholine is highly effective for prompt termination of episodes of paroxysmal supraventricular tachycardia.

2. It is valuable for clearly delineating the mechanism of auricular flutter, especially in the presence of bundle branch block simulating the electrocardiographic appearance of ventricular tachycardia.

The authors wish to express their gratitude to Dr. Edmund F. Foley for his encouragement and counsel. Acetylcholine hydrochloride was generously supplied by Merck, Sharp & Dohme, Rahway, N. J.

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The Use of Triparanol to Lower Serum Cholesterol

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There is a great deal of evidence that a disturbance in cholesterol metabolism plays an important part in the pathogenesis of atherosclerosis. This has stimulated an increasing number of attempts to lower the serum cholesterol. These have included various diets, the substitution or addition of unsaturated fatty acids, the administration of estrogens, thyroid compounds, nicotinic acid, and plant sterols.

We are currently investigating the effect of Triparanol (MER-29*), a synthetic compound which has been introduced as an inhibitor of the biosynthesis of cholesterol. Animal and human radioisotope tracer studies indicate that Triparanol inhibits the biosynthesis of cholesterol in the liver and other tissues.[1,2] The mechanism and exact site of action are unknown, but the site is thought to be between demosterol (a precursor of cholesterol) and cholesterol.[3]

We have treated 64 patients for periods of 1 to 4 months with a single daily dose of 250 mg. These patients consisted of 42 men and 22 women, whose ages ranged from 27 to 85 years. All but 10 of these patients had objective evidence of coronary artery disease. Of the 10 without coronary artery disease, 9 had either hypertension or diabetes, or both. Two to four determinations of serum cholesterol were made before treatment was initiated. Diets were as prescribed by the attending physicians. Many of the patients were on low-fat diets, most had been on such diets for many months prior to the study. A few were on a diet which was low in saturated fats, several were on diabetic diets, several were on low-calorie diets, and several were on unrestricted diets. No change was made in other therapeutic agents which had been prescribed by the attending physician. Serum cholesterols were determined every 30 days after treatment was initiated. The average pretreatment level was 339 mg. per cent. The distribution of the pre- and post-treatment values are summarized in Table I.

Five patients discontinued treatment or were lost to follow-up in less than 30 days, so that no post-treatment value was obtained. One patient discontinued treatment because of severe nausea and vomiting, another discontinued treatment because of giant urticaria which recurred when an attempt was made to resume

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treatment, one patient died, one entered a mental hospital and was lost to follow-up, and another failed to return for a post-treatment cholesterol (no reason was given).

Fifty-nine patients have been treated for periods of from 1 to 4 months and have had 1 to 3 post-treatment determinations of serum cholesterol. Fifty-two, or 88 per cent, have shown a lowering of serum cholesterol; the average drop was 74.4 mg. per cent, or 22 per cent of the pretreatment level. Seven patients showed a rise in serum cholesterol; 6 of these had a rise of less than 31 mg. per cent. Two patients failed to maintain their improvement on continued administration of 250 mg. per day; no attempt was made to try a larger dose. Five failed to improve during the first 30 days, but did improve during the second month on the same daily dose of 250 mg. A summary of the magnitude of the response is shown in Table II.

TABLE I

SERUM LEVEL (MG. %)	NUMBER OF PATIENTS	
	PRETREATMENT	POST-TREATMENT
150–199	1	9
200–249	8	21
250–299	7	11
300–349	26	9
350–399	6	4
400–449	10	4
450–499	4	0
Over 500	2	1

No attempt was made to evalute the effect on the coronary artery disease present in the treated patients. One patient had a documented myocardial infarction while on therapy, and another patient with an old infarct and angina decubitus died suddenly while on therapy, presumably of his disease, but no autopsy was performed. No routine studies were carried out to determine toxicity, and the only bad effects observed were those listed above.

TABLE II. CHANGE IN LEVEL OF SERUM CHOLESTEROL

MAGNITUDE OF CHANGE	NUMBER OF PATIENTS
Drop of 300 mg. or more	1
Drop of 200–299 mg.	0
Drop of 150–199 mg.	1
Drop of 100–149 mg.	14
Drop of 50–99 mg.	21
Drop of 1-49 mg.	16
Rise of 1-49 mg.	5
Rise of more than 50 mg.	1

SUMMARY

This is a preliminary report on the effect of Triparanol in 59 patients treated with 250 mg. of the compound per day. Eighty-eight per cent showed a drop in serum cholesterol; the average was 74.4 mg. per cent. Two failed to maintain their initial improvement. Side effects forced discontinuance of treatment in 2 patients. One patient died, presumably of coronary artery disease, and another had a myocardial infarct while on therapy. A longer period of observation is needed to better evaluate the efficacy and toxicity of Triparanol.

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Hypotensive Action of Bretylium Tosylate (Darenthin)

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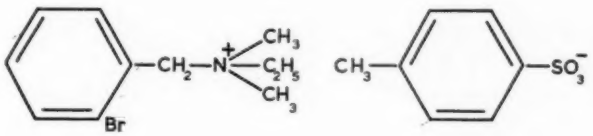
A new type of hypotensive agent, bretylium tosylate (Darenthin) (Fig. 1) has been described by Boura, Copp and Green (cited by Boura and associates[1]). These authors demonstrated by isotope studies that it has the remarkable property of accumulating selectively in adrenergic neurones, in sympathetic ganglia, and in organs with a strong sympathetic innervation. Their evidence suggests that the conductivity of sympathetic nerves is depressed, especially at the endings but to some extent in the nerve trunks. Of great interest is the absence of any significant effect upon the parasympathetic nervous system. Some drug toleration has been demonstrated to several of the actions of the drug in animal experiments.



N–O–bromobenzyl–N–ethyl : N : N–dimethylammonium
p. toluenesulphonate.

Fig. 1.—Bretylium tosylate (Darenthin).

The first clinical trials with bretylium tosylate were conducted by Boura and associates,[1] who found that the substance was suitable for more extended clinical trials. It was evident from their preliminary results and ours (Smirk and Hodge[2]) that, in man, parasympathetic side effects were slight or absent.

We now report a more extended clinical trial on 100 patients, many of whom were given bretylium tosylate because of the prominence of parasympathetic side effects while they were being treated with ganglionic blocking drugs.

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TABLE I

PATIENT NUMBER	DOSE (MG.)	BLOOD PRESSURE (MM. Hg) AND PULSE RATE BEFORE DRUG				BLOOD PRESSURE (MM. Hg) AND PULSE RATE AT TROUGH OF FALL IN BLOOD PRESSURE			
		B.P. (LYING)	PULSE (LYING)	B.P. (STANDING)	PULSE (STANDING)	B.P. (LYING)	PULSE (LYING)	B.P. (STANDING)	PULSE (STANDING)
82	350	180/100	72	178/106	70	178/104	72	140/90	68
1011	250	150/88	66	150/94	64	152/90	70	116/88	74
1356	400	180/118	68	160/98	70	160/110	72	132/98	70
372	300	200/104	66	194/106	72	170/92	68	110/70	78
1192	200	256/110	60	252/108	64	206/108	68	176/98	62
32	150	190/110	70	160/100	72	128/84	58	104/64	54
26	400	204/104	68	180/94	66	180/106	66	140/90	68
305	300	266/118	52	260/110	52	206/98	56	192/94	74
48	200	176/114	90	168/110	92	162/120	90	162/116	96
1367	600	192/100	86	194/104	86	176/96	84	168/94	86
1400	350	160/96	66	168/108	68	160/108	64	120/78	70
1418	450	182/104	66	170/102	60	164/90	64	136/86	60
1166	200	180/116	72	170/110	74	148/94	70	120/96	70
1402	300	200/100	72	188/94	76	166/90	74	148/84	72
62	400	192/110	70	174/100	68	166/90	72	138/80	76
1410	600	172/96	84	160/104	78	168/100	84	154/102	72
Mean	340	192/105	70	182/103	70	168/98	70	141/89	71

METHOD

The period of treatment has ranged from 1 to 8 months. The drug was given orally in 200-mg. tablets, two or three doses daily; the aim was to produce a fall in blood pressure to or near to normal levels in the trough of the fall. The efficacy of drug action was judged by repeated all-day tests at our clinic for hypertensive outpatients or in the wards; the average number of such all-day tests was 15 per patient.

RESULTS

It was found that of the 100 patients, 46 were satisfactorily controlled by bretylium alone; the mean effective dose for these patients was 329 mg. (range, 150 to 600 mg.). Another 24 patients were receiving chlorothiazide, hydrochlorothiazide, or a rauwolfia alkaloid at the time they started to take bretylium tosylate, and the mean effective dose in this group was 278 mg. (range, 100 to 550 mg.). The other 30 patients were not controlled by bretylium tosylate in doses up to 600 mg. three times daily (in one case up to 1,000 mg.). Because of the bulk of drug and its bitter taste these patients were also given a low dose of ganglionic blocking drug in order to complete the control of the blood pressure. By such a combination, resistant cases could be controlled satisfactorily with minimal discomfort from side effects.

Effect of Posture on the Hypotensive Action.—As with ganglionic blocking drugs, the fall in blood pressure which follows the oral administration of bretylium tosylate is greatest when the patient is in the standing posture, of intermediate degree when he is sitting, and least when he is lying down (Table I).

The relationship between the blood pressure of the patient when he is in the standing and in the lying postures is of the same order as that encountered with ganglionic blocking drugs when the degree to which the blood pressure is reduced is similar for the two classes of hypotensive agents.

Effect of Bretylium Tosylate on Pulse Rate.—The effect of bretylium tosylate on pulse rate is slight in most patients, as can be seen from Table I. The mean pulse rate before administration of the drug was 70.5 when the patient was lying down, and 70.8 when the patient was standing up. At the trough of the fall in blood pressure the pulse rates were 70.8 with the patient lying down and 71.9 with the patient standing up. There does not appear to be any consistent change in the pulse rate, although some patients showed a moderate slowing of the pulse at the initiation of therapy with bretylium tosylate. One patient (H 32), while standing, showed a fall in pulse rate from 72 to 54 at the trough of the fall in blood pressure. This was noted on the second day of therapy only; a "trough" blood pressure of 122/82 was reached on the first day, without any alteration in pulse rate. Another patient (H 1192) developed mild angina on the evening of his first day, despite a smaller fall in blood pressure than he had been accustomed to previously with pempidine. The following morning he showed a sinus bradycardia; his pulse rate was 40 per minute, in contrast to 70 per minute on the previous day.

The Effect of Chlorothiazide or Hydrochlorothiazide on the Fall in Blood Pressure After Bretylium Tosylate.—Just as with ganglionic blocking drugs, the dose of bretylium tosylate required to bring the blood pressure to a nearly normal

level may be reduced when patients are given chlorothiazide (500 mg. twice daily) or hydrochlorothiazide (50 mg. twice daily). In 3 patients who were given these adjuvant drugs while on bretylium tosylate the effective single dose of bretylium tosylate fell by an average amount of 150 mg.

The Effect of Reserpine on the Fall in Blood Pressure After Bretylium Tosylate.—The effect of reserpine on the fall in blood pressure after bretylium tosylate has not been clarified satisfactorily, since all patients on this combination of drugs were receiving reserpine prior to commencing bretylium tosylate. Indirect evidence for an increased hypotensive action due to reserpine is that the average single dose for all patients receiving bretylium tosylate alone was 329 mg., whereas the average single dose for patients on bretylium tosylate plus reserpine was 267 mg.

Drug Toleration.—In an attempt to discover whether drug toleration occurs, the dose of bretylium tosylate which first caused a fall in the blood pressure (standing posture) to a normal or nearly normal level is taken as the initial dose. After repeated administration, the amount of the drug required at some later stage to induce approximately the same fall in blood pressure is used as an index of the presence or absence of drug toleration. Alternatively, drug toleration may be indicated by a smaller fall in blood pressure on the same dose. In most instances, at least 10 all-day tests have been performed, and it is upon the basis of all-day tests that a conclusion is reached.

Fully adequate data were obtained for 30 patients. In these patients, tolerance was considered to be absent in 17, doubtful in 4, slight in 4, definite in 5. In general, the increase in dosage is less than twofold, but there have been a few clear exceptions in which larger increases have been required. There were several instances in which the starting dose of bretylium tosylate had to be reduced. Drug toleration is usually of insufficient degree to interfere with the regulation of dosage.

Side Effects.—Hypotensive doses of bretylium tosylate sufficient to reduce the blood pressure when the patient is in the standing posture, to nearly normal levels (usually about 130/85 mm. Hg) at the trough of the fall in blood pressure, have caused few significant side effects; indeed, most patients made no spontaneous complaints.

Side effects due to parasympathetic blockade, such as dryness of the mouth, blurring of near vision, constipation, and impotence, have been minimal or absent in nearly all patients treated—even in those for whom such symptoms had proved to be a major problem with previous ganglionic blocking therapy. Constipation was in most cases relieved; mild looseness of the bowels was noted by 20 per cent of the patients, and hyperactive bowel sounds by 40 per cent. Indigestion developed or became worse with bretylium tosylate in 15 per cent of the patients—this was never severe enough to warrant discontinuing treatment.

Only one patient continued to experience blurring of vision which, although less severe, was indistinguishable in timing and character from that due to the previous administration of pempidine. Nevertheless, approximately half of all the patients who were receiving bretylium tosylate admitted, on questioning, to some symptoms referable to the eyes. These could be grouped as: *nonvisual,*

including sensations described variously as "heavy," "pressing," "lifting," or "pulsing" feelings over or behind the eyes, soreness of the eyeballs, and irritation of the conjunctivae, often accompanied by mild suffusion and increased lacrimation; and *visual*, with blurring of both near and distant vision, often coming in attacks lasting only a few minutes, which could sometimes be overcome by voluntary concentration, and which were sometimes, but not always, maximal at the time of the maximal fall in blood pressure. Because of its variable character this visual blurring could not be satisfactorily overcome with lenses, but it was never severe enough to constitute an important problem in management. Although the relationship of the orthosympathetic innervation to accommodation of vision is less clearly defined than that of the parasympathetic, these clinical observations suggest that one of its functions may be to exert a stabilizing effect on control of accommodation.

Flashes of color at the periphery of both visual fields were noted regularly by one patient at the time of maximum drug action.

Significant nasal congestion was noticed by 40 per cent of the patients receiving bretylium tosylate, and mild to moderate polyuria by a similar number. One symptom encountered in nearly a quarter of the patients questioned was pain over the region of the parotid glands, often aggravated at mealtimes. This has not been associated with reduction in the formation of saliva, and the cause is still obscure. This symptom is usually not compained of spontaneously.

Duration and Predictability of Action.—All-day tests indicate that the effect of an oral dose of a magnitude sufficient to reduce the blood pressure to a nearly normal level when the patient is standing up may pass off in 5 or 6 hours. In some patients, however, the effect of a single dose may last over 16 hours, and a large dose at night may lead to appreciable hypotension next day.

Adequate 24-hour coverage is normally achieved by three daily doses—less frequently, omission of the midday dose is possible. The hypotensive response of the patient to bretylium tosylate, when the dose is large, appears to be less predictable than the response to the highly potent ganglionic blockers, such as mecamylamine, pempidine, trimethidinium, and certain ganglionic blocking drugs chemically related to pempidine which are on clinical trial, such as M & B 4500 and M & B 5409A.

Beyond question, the new hypotensive agent, bretylium tosylate, is of great interest. We have found it to be the hypotensive agent of choice for some patients. In other patients the large dose and a degree of unpredictability of action have proved disadvantageous when bretylium tosylate is used alone. However, the requisite dose may be somewhat reduced by combination with chlorothiazide or hydrochlorothiazide, and probably also by combination with reserpine. Alternatively, the combination of a potent ganglionic blocking drug and bretylium tosylate can usually be given in proportions which reduce the blood pressure adequately without causing significant parasympathetic side effects.

SUMMARY

1. Bretylium tosylate has been employed alone or in combination in the treatment of 100 patients with arterial hypertension.

2. It does not lead to significant parasympathetic side effects, such as dry mouth, constipation, or impotence; it occasionally causes looseness of the bowels, which is probably due to lowered orthosympathetic activity.

3. Most patients prefer bretylium tosylate to ganglionic blocking drugs.

4. The main disadvantages are: (a) a peculiar visual blurring which subjectively differs from that which follows the use of ganglionic blocking drugs, (b) the large dose which is needed in some patients, (c) occasional unpredictability of absorption, (d) occasional indigestion, and (e) facial pain on eating.

5. Bretylium tosylate may be combined advantageously with rauwolfia alkaloids or hypotensive diuretics such as hydrochlorothiazide. In patients requiring large doses of bretylium tosylate, potent ganglionic blocking drugs, such as pempidine, M & B 5409A, M & B 4500, or mecamylamine, in appropriate doses, may be used to replace a proportion of the bretylium tosylate, without causing parasympathetic side effects.

We are indebted to the Wellcome Foundation, Ltd., for generous supplies of bretylium tosylate.

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Experimental and Laboratory Reports

Myocardial Infarct-Like Lesions Produced by Histamine Liberators in Rats. Preliminary Report

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Acute myocardial lesions which resemble myocardial infarction have been produced by several techniques in rats. In some cases the lesions were caused by the administration of substances normally present in the tissues, namely, adrenaline,[1] histamine,[2] and hormones.[3] The so-called histamine liberators are known to produce important changes in blood pressure and lesions in the stomach and intestines in rats.[4,5] The effect of these substances is very similar to that of the injection of exogenous histamine and, to a lesser extent, the injection of serotonin.

Since the exogenous administration of pressor amines is capable of producing myocardial lesions, it seemed possible that lesions might also be produced by the injection of histamine liberators.

The purpose of this paper is to describe a new method for eliciting myocardial lesions which resemble myocardial infarction, by means of histamine liberators in acute experiments performed in rats.

METHODS

Experiments were carried out on male Wistar rats which weighed 200 to 250 grams each. The intact animal was injected intraperitoneally with polymyxin B at a dose of 1.5 mg. per kilogram of body weight dissolved in distilled water at a concentration of 0.1 mg./ml. During the first 4 hours the animals were carefully observed for signs of histamine liberation. They were kept in large cages and had free access to food and drinking water. They were sacrificed by decapitation 24 hours after the administration of polymyxin B, which was given always in a single injection. The mortality rate was 20 per cent. A total of 80 rats was used, divided into groups of 5 animals each, with a matching group of the same number as a control.

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A 12-lead electrocardiogram was recorded in 5 animals before the injection of polymyxin B. In the 4 surviving rats the electrocardiograms were recorded 48 hours and 9 days after the injection, and the animals were then sacrificed. In order to facilitate the recording of the tracings, the rats were anesthetized with sodium Amytal (9 mg. per 100 grams of body weight intraperitoneally), and the polymyxin B was given 24 hours later. The same procedure was followed every time that the electrocardiograms were recorded, except that no more polymyxin B was given. Immediately after the rats were sacrificed, the heart was taken out and placed in SUSA fixative, and later was stained with hematoxylin and eosin for histopathologic study.

Fig. 1.—Rat No. 60, sacrificed 24 hours after 1.5 mg./Kg. of polymyxin B had been given intraperitoneally. Zone of white discoloration at the apex corresponds to the site of the lesion.

RESULTS

A few minutes after the injection of polymyxin B, all the animals showed signs of histamine liberation (itching, hyperemia of snout and paws, cyanosis, and polypnea). Approximately 30 minutes later the majority of the rats were in shock, and some of them died during this period. Autopsy of the sacrificed animals revealed a marked congestion of the liver, intestines, and spleen and gastric ulcerations in all the animals. The heart appeared darker than normally, and the coronary vessels seemed to be dilated. At the apex of the heart in 90 per cent of the animals there was a whitish discoloration which ranged in size from pin-point to 3 to 4 $mm.^2$ in surface area (Fig. 1). It is important to mention the fact that we could not observe lesions with the naked eye in other portions of the heart. Microscopically, all of the hearts showed lesions of varying degree, most marked in the subendocardial and epicardial segments of the apex and the surrounding regions. There was a loss of the transverse striation of the myocardial fibers, destruction of the sarcoplasm, and intense infiltration by inflammatory cells (Fig. 2). The capillaries appeared to be dilated, and we could not find any vascular obstruction nor intimal changes in the vessels surrounding the lesion. In some microscopic fields the destruction of the myocardium was massive.

All of the electrocardiograms which were recorded before the rats were treated with polymyxin B showed the normal pattern for rats, and all tracings showed signs of myocardial necrosis after the injection. The histopathologic

findings were as described before. The most important changes were in the precordial leads: appearance of a deep Q wave, decrease in the voltage of the R wave, with depression of the S-T segment in the right precordial leads and elevation of the S-T segment in the left precordial leads. Several animals had transient arrhythmias, such as auricular flutter and ventricular extrasystoles. Tracings which show these changes in the same rat are presented in Figs. 3, 4, and 5.

DISCUSSION

The previous work of several investigators[1,2] has demonstrated that parenteral administration of certain amines produces myocardial lesions which resemble infarction. Our experimental data show that similar lesions can be produced by the action of endogenous amines liberated by specific substances.

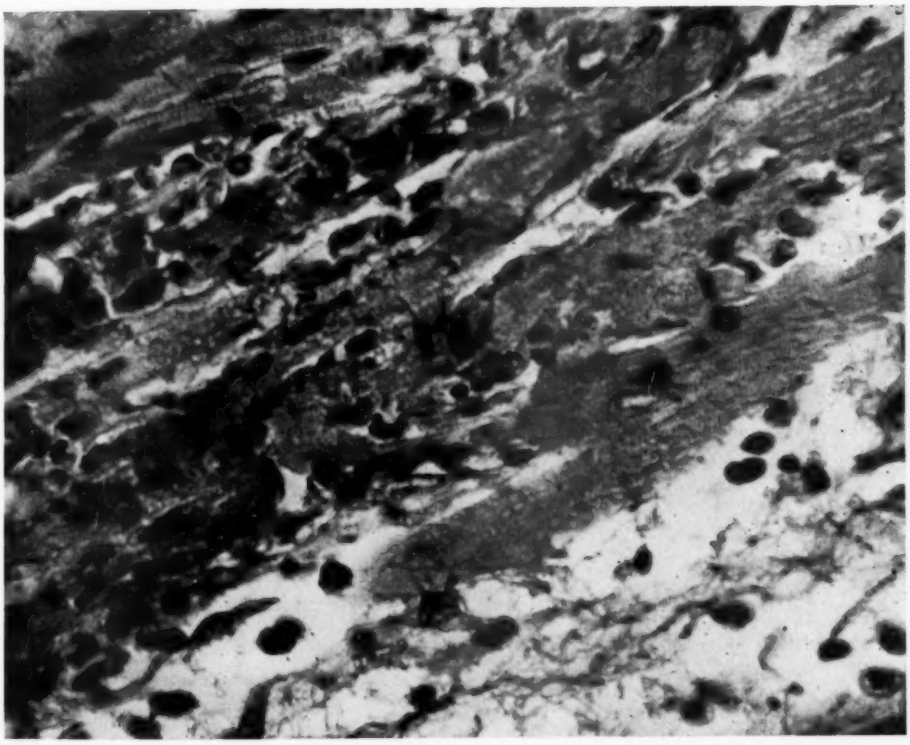

Fig. 2.—Rat No. 3. Section of the heart, showing transverse striation of the myocardial fibers, loss of the striation, destruction of sarcoplasm, and infiltration by inflammatory cells (hematoxylin-eosin stain; magnification ×150, reduced ¼).

These lesions are regularly produced but they vary in extent and degree. The fact that the control groups did not show myocardial necrosis, and that the electrocardiograms permitted us to use the same animal as its own control, made us rule out the spontaneity of these lesions.

In the mechanism of production of these lesions we have to consider two factors: shock and liberation of amines. Since shock is probably accompanied by a decrease in coronary blood flow, it may act as an accessory factor in causing

myocardial lesions. It is a known fact that the administration of histamine liberators to rats produces gastric and appendiceal lesions.[5] It is probable that in the mechanism of production of myocardial lesions with histamine liberators the endogenous amines act in a way similar to injected exogenous amines to damage the muscle fiber. The fact that we were not able to find obstructions in the coronary arteries nor important changes in the different vascular structures does not rule out ischemia as a factor in the pathogenesis of these lesions, but suggests that some other mechanisms are involved.

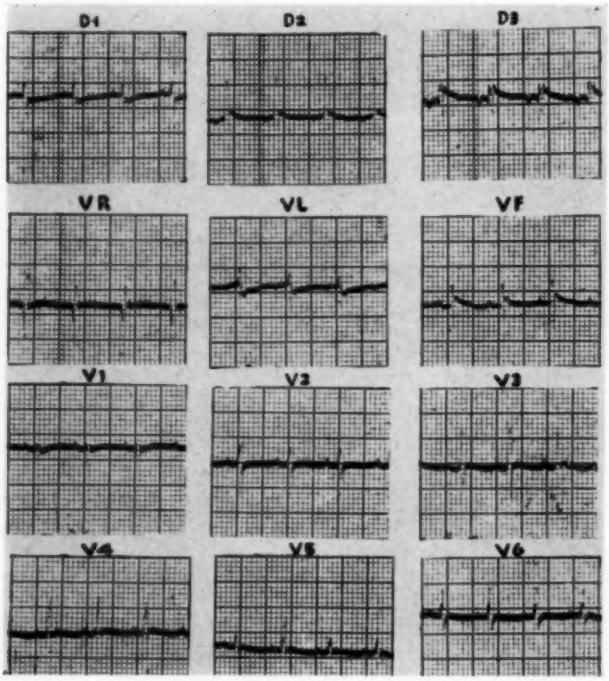

Fig. 3.—Rat No. 45. Control electrocardiogram (paper speed, 50 mm. per second).

The results of further experiments which attempt to identify the endogenous amine will be published elsewhere.[6]

The method described provides a new technique for the production of myocardial necrosis without the use of any conditioning pretreatment. It is simple and predictable, and even though the histologic picture is not exactly like that seen in myocardial infarction due to ischemia, we think that the studies derived from it may shed some light on the pathogenic role of endogenous amines in the genesis of this type of myocardial lesion.

SUMMARY

Myocardial lesions which resemble myocardial infarction have been successfully produced by intraperitoneal injection of polymyxin B in rats. Lesions were visible macroscopically as early as 24 hours after treatment and were always located at the apex. Histologically, they were characterized by loss of striation

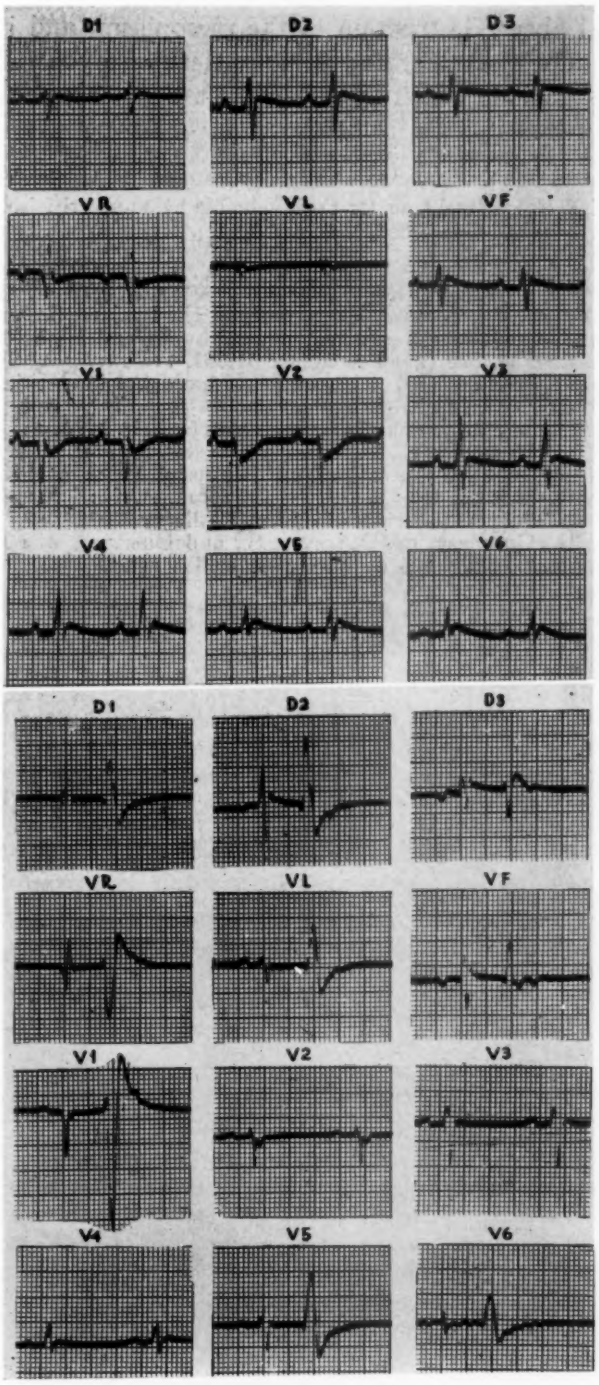

Fig. 4.

Fig. 5.

Fig. 4.—Rat No. 45. ECG taken 48 hours after intraperitoneal injection of 1.5 mg./Kg. of polymyxin B. The P wave became positive in Leads II and III, a deep Q wave appeared in V_1, and there was a sharp decrease in R-wave voltage in V_2. The S-T segment became negative in V_1 and V_2 and elevated in the rest of the precordial leads. (Paper speed, 100 mm. per second.)

Fig. 5.—Rat No. 45. ECG taken 9 days after the injection. The Q wave persisted in Lead V_1. S-T depression in V_1 and V_2 is less marked, and S-T elevation in V_3, V_4, V_5, and V_6 disappeared. Bigeminy developed. (Paper speed, 100 mm. per second.)

of the myocardial fibers, destruction of the sarcoplasm, and infiltration by inflammatory cells. The electrocardiographic pattern of myocardial infarction was found in all the animals in which tracings were taken. Transient auricular flutter and ventricular extrasystoles were observed.

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Some Circulatory Effects of Experimental Hypovolemic Anemia

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INTRODUCTION

Studies by Witham, Fleming and Bloom[1] and by Fleming and Bloom[2] have shown that the infusion of dextran in man is associated with hemodilution anemia, increased plasma volume, and increased cardiac output. Similar effects were found in the dog by Gowdey and Young[3] and by Fowler, Franch, and Bloom.[4] In a previous paper,[5] observations on the relationship of right atrial transmural pressure to right ventricular stroke volume after an exchange infusion of dextran during hypervolemia suggested that there was no consistent relationship between these two variables. The purpose of the present study is to observe the relationship between right atrial transmural pressure and right ventricular stroke work during a state of hypovolemic anemia in dogs, with hypovolemia produced by bleeding, and hypovolemic anemia then being produced in the same animals by an exchange infusion of dextran. The observations reported here indicate that right ventricular stroke work may be increased by anemia during hypovolemia without an increase in right atrial transmural pressure.

METHOD

Studies were made upon 14 dogs under morphine-chloralose anesthesia. Each animal received an initial dose of morphine sulfate, 3 mg. per kilogram subcutaneously, followed by 28 to 70 mg. per kilogram of chloralose intravenously. Supplemental chloralose was given to keep the level of anesthesia constant; the total amount of chloralose given was from 56 to 115 mg. per kilogram. Paired determinations were made of cardiac output, heart rate, stroke volume, right atrial transmural pressure, pulmonary arterial pressure, and systemic arterial pressure during each of three periods: (1) control, (2) after bleeding 20 ml. per kilogram of body weight, and (3) after an exchange infusion of 60 ml. per kilogram of 6 per cent isotonic dextran in saline† with added electrolytes. A volume of blood was withdrawn during the infusion of dextran equal to the volume of dextran infused plus 100 ml. Sufficient KCl, $CaCl_2$, and $MgCl_2 \cdot 6H_2O$ were added to the isotonic dextran in saline to give a concentration of potassium, 15.6 mg. per 100 ml., calcium, 10 mg. per 100 ml., and magnesium, 2 mg. per 100 ml., in the infused dextran. These electrolytes

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were added because of the hyponatremia and hypocalcemia produced by infusion of 6 per cent dextran with 5 per cent dextrose in each of 2 dogs studied in preliminary experiments (see results).

Cardiac output was measured by the Fick principle. Three-minute samples of expired air were collected in Douglas bags by tracheal intubation. The air was analyzed in the Scholander micro-gas analyzer, duplicates checking within 0.04 volume per cent. Simultaneous samples of heparinized pulmonary arterial and systemic arterial blood were collected over a period of 1 minute during the collection of expired air. As blood was withdrawn, it was replaced by an equal volume of donor blood infused into the femoral vein in order to avoid alteration in hemodynamics as pressures and cardiac output were being measured. Blood samples were analyzed in the Van Slyke manometric apparatus for oxygen; paired samples or duplicates checked within 0.2 ml. per 100 ml. Gas volumes were measured in a wet test meter. Stroke volume was determined by dividing cardiac output per minute by heart rate per minute.

Right atrial and pulmonary arterial pressures were measured through No. 7 or No. 8 cardiac catheters inserted during fluoroscopy; systemic arterial pressure was recorded from a carotid artery through a No. 12 metal cannula; intrapleural pressure was recorded through a No. 12 metal cannula with side holes near the tip. Right atrial and intrapleural pressures were detected with Statham P23BB transducers; pulmonary and systemic arterial pressures were detected with Statham P23Db transducers and recorded simultaneously with electrocardiograms upon a Sanborn eight-channel direct-writing recorder. A point 5 cm. above the animal board was used as a zero level for measurements of right atrial and pulmonary arterial pressures. Pressures were recorded continuously during the 3-minute collection of expired air for determination of cardiac output. Right atrial transmural pressure was determined as observed right atrial mean pressure less mean intrapleural pressure.

Blood volumes were measured in 11 dogs during the control period and after the period of exchange infusion of dextran during hypovolemia. Blood volumes were measured with Cr^{51}-tagged red cells, using a modification of the method described by Beierwaltes, Johnson, and Solari.[6]

Serum sodium and potassium were determined by flame photometry, using a Weichselbaum-Barney flame photometer. Serum magnesium was measured by the method of Briggs.[7] Serum calcium was measured by a colorimetric modification of the method of Clark and Collip.[8] Serum osmolality was determined with a Fiske osmometer. Determinations of viscosity were made upon three samples of dog blood and upon dextran, using a Hellige Viscometer No. 1200. Chlorides were determined by the Van Slyke modification of the Volhardt-Harvey method.[9]

Right ventricular stroke work in gram-meters was calculated from the following formula[10]:

$$RVSW = \frac{CO \times 1.055 \times (PA_m - RA_m) \times 13.6}{\text{Heart Rate}}$$

where RVSW = right ventricular stroke work in gram-meters; PA_m = mean pulmonary arterial pressure in mm. Hg; RA_m = mean right atrial pressure in mm. Hg; CO = cardiac output in liters per minute; 1.055 = specific gravity of blood; and 13.6 = specific gravity of mercury.

The specific gravity of the dextran used in these experiments was 1.030 at 37°C. Failure to correct for a decrease in the specific gravity of the circulating blood after the infusion of dextran led to a slight overestimation of right ventricular stroke work during anemia. However, the maximum possible error from this source would be 2.4 per cent and is, therefore, believed to be not significant.

Standard deviations, standard errors, and regression coefficients were calculated by accepted formulae.[11] The significance of regression coefficients and of differences in mean values were determined by the "t" test.[11] Values for p of less than 0.05 were considered to be significant. The averages of paired samples were used in the statistical calculations.

In preliminary experiments, studies were made with 6 per cent isotonic dextran in 5 per cent dextrose solution. Observations were made on changes in serum electrolytes and osmolality in 2 animals who were bled while receiving an equal volume of dextran intravenously. Animal No. 1 weighed 14.8 kilograms and received an exchange infusion of 960 ml. of 6 per cent dextran in 5 per cent dextrose. Animal No. 2 weighed 16.6 kilograms and received 1 L. of 6 per cent dextran in 5 per cent dextrose as an exchange infusion.

RESULTS

Electrolytes and Osmolality.—The results of the studies of serum electrolytes and osmolality in 2 dogs receiving exchange infusions of 6 per cent dextran in 5 per cent dextrose are presented in Table I. It may be seen that the most striking decrease in serum electrolytes were in sodium and calcium, with a lesser decrease in magnesium and in chloride. Five minutes after completion of the exchange, the serum sodium decreased 35 mEq. per liter in Dog No. 1 and 37 mEq. per liter in Dog No. 2. At the same time, serum calcium had decreased 4.3 mg. per 100 ml. in Dog No. 1 and 4.4 mg. per 100 ml. in Dog No. 2. Values had begun to increase at 30 minutes after completion of the infusion, and levels of sodium were approaching normality in 2 to 4 hours; however, levels of serum calcium were still appreciably below normal at 24 and 48 hours. Serum osmolality declined moderately in Dog No. 1, reaching a nadir of 270 milliosmolals per liter at 4 hours, and rising to 291 milliosmolals per liter at 24 hours. The osmolality of the 6 per cent dextran in saline with added electrolytes used in the ensuing studies was 312 milliosmolals per liter.

TABLE I. EFFECT OF EXCHANGE INFUSION OF 6 PER CENT DEXTRAN IN 5 PER CENT DEXTROSE UPON SERUM ELECTROLYTES AND OSMOLALITY

	Na(mEq./L.)	K(mEq./L.)	Ca(mg./100 ml.)	Mg(mg./100 ml.)	mOsm./L.	Cl(mEq./L.)
Dog No. 1						
Control	148	3.8	10.1	1.64	299	108
5 min.	113	4.1	5.8	1.14	300	88
30 min.	125	3.2	6.5	1.25	294	94
1 hr.	129	3.2	7.5	1.35	296	105
2 hr.	134	3.7	7.4	1.45	281	
3 hr.	136	4.0	7.1	1.46	279	103
4 hr.	136	4.1	7.5	1.31	270	102
24 hr.	145	4.1	7.9	1.77	291	103
48 hr.	139	4.2	7.3	1.01		
6 per cent dextran in 5 per cent dextrose					300	
Dog No. 2						
Control	153	4.1	10.0	1.79		119
5 min.	116	4.1	5.6	0.92		86
30 min.	125	3.6	6.5	1.08		86
1 hr.	129	3.9	7.0	1.17		95
2 hr.	139	3.8	6.9	1.40		92
3 hr.	139	3.7	7.3	1.43		96
4 hr.	139	3.7	7.5	1.35		96
Blood removed	121	3.8	6.1	1.21		88

Viscosity.—Table II shows the results of studies on dog blood and on dextran. Viscosities were measured at room temperatures and were corrected to 37°C. It may be seen that the ratios between blood and dextran viscosities were from 1.12 to 1.31, the ratio being greatest when the hematocrit of the dog's blood was highest (50 per cent).

TABLE II. VISCOSITY OF DOG BLOOD AND 6 PER CENT DEXTRAN IN SALINE

	HEMATOCRIT (%)	VISCOSITY (CENTIPOISE)	BLOOD/DEXTRAN VISCOSITY RATIO
Dextran	—	3.54	—
Dextran	—	3.55	—
Dog Blood No. 1	36	3.97	1.12
Dog Blood No. 2	40.5	4.34	1.23
Dog Blood No. 3	50	4.65	1.31

Cardiac Output, Arteriovenous Oxygen Difference, Heart Rate, Stroke Volume.—The results of paired observations of cardiac outputs, oxygen consumptions, arteriovenous oxygen differences, heart rates, and stroke volumes in each of the three periods—control, hypovolemia, and hypovolemic anemia—in 2 representative dogs are shown in Table III. For technical reasons, only a single set of observations was made during the hypovolemic anemic period in 2 animals. The changes in arteriovenous oxygen difference and in cardiac output were consistent. In each animal, arteriovenous oxygen difference increased during the hypovolemic period and decreased during the hypovolemic anemic period.

TABLE III. EFFECT OF HYPOVOLEMIA AND OF HYPOVOLEMIC ANEMIA ON CARDIAC OUTPUT AND STROKE VOLUME IN 2 REPRESENTATIVE DOGS

DOG NO., AND WEIGHT (Kg.)	O_2 CONSUMPTION (ML./MIN.)	A-V O_2 DIFFERENCE (ML./100 ML.)	CARDIAC OUTPUT (L./MIN.)	CARDIAC OUTPUT (ML./Kg./MIN.)	HEART RATE (MIN)	STROKE VOLUME (ML)	HEMATOCRIT (%)
56(14.6) Control	69	4.3	1.590	109	68	23.4	46.5
	65	5.4	1.208	83	44	27.5	46.5
Hypovolemia	58	7.5	0.783	54	40	19.6	44
	61	7.6	0.812	56	36	22.6	44
Hypovolemic anemia	63	2.7	2.299	158	96	24.0	14
	61	2.5	2.402	165	82	29.3	14
84(17.9) Control	107	5.7	1.885	105	93	20.3	45.5
	118	6.3	1.883	105	72	26.2	—
Hypovolemia	104	9.3	1.114	62	170	6.6	44
	100	9.1	1.098	61	176	6.2	42.5
Hypovolemic anemia	89	3.5	2.527	141	192	13.2	12.5
	88	3.5	2.489	139	159	15.7	—

As shown in the statistical Table V, the increase in arteriovenous oxygen difference during hypovolemia was significant at the $p < 0.001$ level. The decrease in arteriovenous oxygen difference during hypovolemic anemia was significant at the $p < 0.001$ level when compared with either the hypovolemic period or with the control period. The cardiac outputs also showed consistent changes, falling in each animal during hypovolemia and increasing in each animal during hypovolemic anemia. A graph indicating representative changes in circulatory dynamics in one animal, Dog No. 56, during hypovolemia and hypovolemic anemia is shown in Fig. 1. The decrease in cardiac output during hypovolemia and

the increase in cardiac output during the period of hypovolemic anemia as compared with either the hypovolemic or control periods were each significant at the $p < 0.001$ level (Table V). The heart rate increased over the control during hypovolemia in 12 of the 14 animals; the mean increase was significant, $p < 0.001$ (Table V). In some animals there was no further increase in heart rate during hypovolemic anemia, although the mean increase of 25 beats per minute was of significance ($p < 0.025$) statistically (Table V). The changes in stroke volume were also consistent. There was a decline in stroke volume in each animal during hypovolemia, and an increase in stroke volume over the previous period during hypovolemic anemia. Mean values for the change in stroke volume are presented in Table V, where it may be seen that the decline in stroke volume during hypovolemia and the increase in stroke volume during hypovolemic anemia were each significant at the $p < 0.001$ level. The stroke volume during hypovolemic anemia was, however, significantly lower than during the control period, $p < 0.01$.

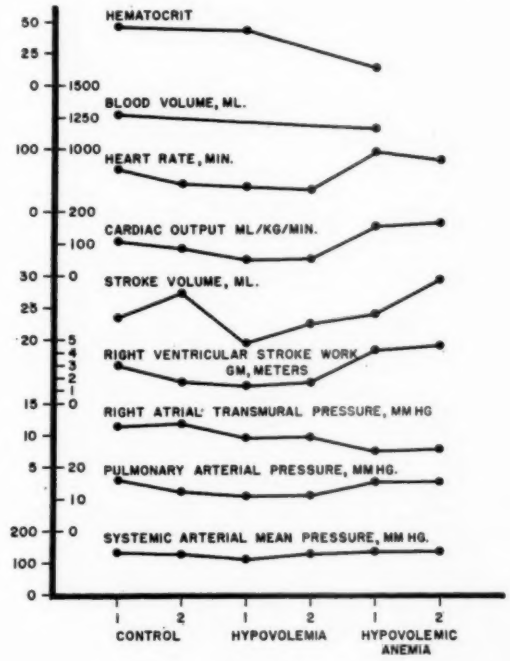

Fig. 1.—Circulatory response of Dog No. 56 to hypovolemia and to hypovolemic anemia.

Hematocrits.—Hematocrits were 39 to 56.5 per cent during the control period. The changes in hematocrit during hypovolemia were variable; some animals showed a slight decrease, and others showed a slight increase. During hypovolemic anemia, hematocrits were from 12.5 to 21 per cent. The mean of hematocrits was 48.4 per cent during control, 48.9 per cent during hypovolemia, and 16.2 per cent during hypovolemic anemia (Table V).

Right Heart Pressures, Stroke Work, Blood Volume.—The effects of hypovolemia and hypovolemic anemia upon intrapleural, right heart, systemic arterial pressures, right ventricular stroke work, and blood volume in 2 representa-

tive dogs are presented in Table IV. During hypovolemia, pulmonary arterial pressure fell in 6 animals, was essentially unchanged in 3, and rose in 1. During hypovolemic anemia, pulmonary arterial mean pressure rose in 6 animals and was essentially unchanged in 5. During hypovolemia, right atrial mean pressure fell in 13 animals and was essentially unchanged in 1. The mean decrease of 1.21 mm.Hg was significant, $p < 0.001$ (Table V). During hypovolemic anemia the changes in right atrial mean pressure were variable: 8 animals showed essentially no change, 4 showed an increase, and 2 showed a decrease. The mean increase of 0.04 mm.Hg was not significant, $p > 0.5$. The right atrial mean pressure was significantly lower during hypovolemic anemia than during the control period, $p < 0.001$. Intrapleural pressures showed no consistent changes during the periods of hypovolemia and hypovolemic anemia.

TABLE IV. EFFECT OF HYPOVOLEMIA AND OF HYPOVOLEMIC ANEMIA UPON RIGHT HEART, SYSTEMIC ARTERIAL, AND INTRAPLEURAL PRESSURES AND UPON RIGHT VENTRICULAR STROKE WORK IN 2 REPRESENTATIVE DOGS

DOG NO., AND WEIGHT (Kg.)	PA(MM. Hg)	RA(MM. Hg)	PLEURA (MM. Hg)	CA(MM. Hg)	RA TRANSMURAL (MM. Hg)	RVSW (GM.-METER)	BLOOD VOLUME (ML.)
56(14.6) Control	16	7.1	—4.2	135	11.3	2.99	1,279
	12	7.7	—4.2	125	11.9	1.69	
Hypovolemia	11	6.1	—3.5	112	9.6	1.38	
	11	6.1	—3.6	125	9.7	1.60	
Hypovolemic anemia	15.5	3.5	—4.0	137	7.5	4.12	1,165
	15.5	4.7	—3.1	137	7.8	4.54	
84(17.9) Control	13	4.2	—4.4	130	8.7	2.55	1,161
	12.5	3.6	—4.9	135	8.5	3.32	
Hypovolemia	21	2.9	—5.1	100	7.9	1.71	
	20	2.7	—5.2	97	8.0	1.55	
Hypovolemic anemia	20	4.1	—4.0	105	8.1	3.01	1,042
	13.5	3.8	—4.1	113	7.9	2.17	

PA: Pulmonary arterial mean blood pressure. RA: Right atrial mean blood pressure. CA: Carotid arterial mean blood pressure. RVSW: Right ventricular stroke work.

Right atrial transmural pressures during hypovolemia decreased in 13 animals and rose in 1. The mean decrease of 1.22 mm.Hg was significant, $p < 0.005$ (Table V). During hypovolemic anemia the changes in right atrial transmural pressure were more variable: 8 animals showed a decrease, 3 showed an increase, and 3 showed essentially no change. The mean decrease of 0.7 mm.Hg was not significant, $p > 0.05$ (Table V). Right atrial transmural pressure was significantly lower during the period of hypovolemic anemia than during the control period, $p < 0.005$ (Table V).

During hypovolemia, right ventricular stroke work fell in 9 animals and was essentially unchanged in 2. Calculations of this variable were not made in the other 3 animals because pulmonary arterial pressures were not measured. Right ventricular stroke work declined significantly during hypovolemia, $p < 0.005$ (Table V). During the period of hypovolemic anemia, right ventricular stroke work rose in each of the 11 animals, as compared to that of the period

of hypovolemia. The mean increase was of statistical significance, $p < 0.05$ (Table V). As compared with that of the control period, right ventricular stroke work during hypovolemic anemia showed a decrease in 5 animals, an increase in 4, and essentially no change in 2. There was no significant relation between changes in right ventricular stroke work and changes in right atrial transmural pressure during the periods of hypovolemia and hypovolemic anemia, $p > 0.5$ (Table V).

Of the 11 animals in which measurements were made, Cr^{51} blood volumes fell during hypovolemic anemia in 9 animals, as compared with control values. In 2 animals, blood volumes were essentially unchanged. In each animal the decrease in measured blood volume was less than the total volume removed from the animal.

TABLE V. STATISTICAL TABLE

	CONTROL	HYPOVOLEMIA	MEAN DIFFERENCE ± S.E.	HYPOVOLEMIC ANEMIA	MEAN DIFFERENCE ± S.E.	HYPOVOLEMIC ANEMIA VS. CONTROL (MEAN DIFFERENCE ± S.E.)
Cardiac output (L./min.)	1.935	1.207	−0.728 ± 0.107 $p < 0.001$	2.807	+1.600 ± 0.136 $p < 0.001$	+0.872 ± 0.141 $p < 0.001$
Arteriovenous O_2 difference (ml./100 ml.)	6.27	9.02	+2.76 ± 0.285 $p < 0.001$	4.07	−4.95 ± 0.337 $p < 0.001$	−2.20 ± 0.271 $p < 0.001$
Blood volume (ml.)	1,410			1,192	−218 ± 45.2 $p < 0.001$	
Heart rate (min.)	84	134	+50.7 ± 10.9 $p < 0.001$	159	+25 ± 9.42 $p < 0.025$	
Stroke volume (ml.)	25	11.2	−13.8 ± 1.71 $p < 0.001$	18.7	+7.6 ± 0.935 $p < 0.001$	−6.3 ± 1.935 $p < 0.01$
Right atrial mean pressure (mm. Hg)	4.6	3.38	−1.21 ± 0.153 $p < 0.001$	3.42	+0.04 ± 0.215 $p > 0.5$	−1.18 ± 0.252 $p < 0.001$
Right atrial transmural pressure (mm. Hg)	9.46	8.25	−1.22 ± 0.289 $p < 0.005$	7.55	−0.7 ± 0.362 $p < 0.1, > 0.05$	−1.91 ± 0.509 $p < 0.005$
Hematocrit (%)	48.4 ± 5.37 (S.D.)	48.9 ± 4.83 (S.D.)		16.2 ± 2.71 (S.D.)		
Right ventricular stroke work (Gm.-meter)	3.22	1.32	−1.9 ± 0.509 $p < 0.005$	3.26	+1.9 ± 0.743 $p < 0.05$	+0.04 ± 0.534 $p > 0.5$
Regression of change in right ventricular stroke work on change in right atrial transmural pressure	$b = 0.000192879$;	$S_b = 0.0003671$;	$t = 0.5254$;	$p > 0.5$		

DISCUSSION

From the results described in the foregoing section, three conclusions may be drawn: (1) There was significant hyponatremia and hypocalcemia when 6

per cent dextran in 5 per cent dextrose was used as an exchange infusion. (2) When 6 per cent dextran in saline was used as an exchange infusion, cardiac output was increased by anemia even when the blood volume was diminished. (3) Right ventricular stroke volume and stroke work were increased by anemia in the absence of a rise in right atrial transmural pressure.

Blood Electrolyte Alterations.—The immediate decrease in blood sodium and calcium after bleeding and exchange infusion with dextran in 5 per cent dextrose may be attributed to a loss of electrolytes in the removed blood, and the infusion of a nonelectrolyte-containing substance which remains within the intravascular space in appreciable quantities for 96 hours or more.[12] The persistent hypocalcemia may be explained by the decrease in serum protein known to occur after bleeding with dextran replacement.[13] The gradual decline in plasma osmolality may be explained on the basis of persistent decrease in serum protein with the appreciable fall in levels of serum dextran which is known to occur from 4 to 6 hours after infusion of dextran.[12,13] These observations may be of importance in patients with shock due to loss of blood who may be treated with dextran in 5 per cent dextrose.

Changes in Blood Volume.—Although the data show clearly that cardiac output may be increased by anemia in the presence of decreased blood volume, the measured blood volumes after bleeding and infusion of dextran were consistently higher than would be expected from the amount of blood removed. Failure of measured blood volume to fall as greatly as suggested from the amount removed could be due to several factors. After the original period of bleeding, some replenishment of depleted vascular volume occurs by splenic contraction and by movement of fluids from the extravascular space. In addition, the dextran with added electrolytes was somewhat hypertonic and would be expected to bring increased amounts of water into the intravascular space. Another factor of importance could be a moderate error in the technique of measuring blood volume, since anemia may be associated with alteration of the relationship between the large vessel and body hematocrit.[14] This source of error should be minimized by the fact that arterial blood hematocrits were measured in the present study, but it could still be a factor.

Mechanism of Increased Cardiac Output in Anemia.—The mechanism of increased cardiac output in acute anemia is not greatly clarified by these studies. Although the decrease in blood viscosity produced by dextran is undoubtedly a factor, the alterations in viscosity are insufficient to explain the magnitude of the observed changes in cardiac output. Theoretically, if a dog's blood with an hematocrit of 50 per cent were completely replaced by dextran, the viscosity would be expected to decrease from 4.65 to 3.54 centipoise at 37°C. On the basis of the Poiseuille equation, this change in viscosity would be expected to increase cardiac output by 31 per cent if circulation could be maintained. However, during hypovolemic anemia, mean cardiac output increased by 133 per cent over that in the preceding hypovolemic period. The increase in cardiac output during anemia with hypovolemia was due to an increase both in stroke volume and heart rate. Since the stroke volume was lower than control stroke volume, the increase in cardiac output during hypovolemic anemia over the control was

due to tachycardia alone. The increase in stroke volume during hypovolemic anemia over that in hypovolemia would appear to be unrelated to an increase in the filling pressure of the right heart. Sunahara and Beck[15] observed increased cardiac output without rise in right atrial pressure in bled dogs given plasma infusions. Fleming and Bloom[2] reported poor correlation between the change in right atrial pressure and the change in cardiac output in human subjects receiving infusions of dextran. Studies of Justus, Cornett and Hatcher[16] have suggested that a humoral mechanism may be involved in the increased cardiac output observed during acute anemia in dogs.

Mechanism of Increased Ventricular Stroke Work.—The increase in right ventricular stroke work without an increase in right atrial transmural pressure during hypovolemic anemia requires further explanation. Among the factors to be considered are: the reliability of atrial transmural pressure as an index of diastolic ventricular pressure, the reliability of end-diastolic ventricular pressure as an index of diastolic ventricular volume, the influence of alteration in heart rate upon the relationship of stroke work to atrial transmural pressure, and the possibility of increase in cardiac contractility due to anemia, enabling increased stroke work to be performed without increasing the length of cardiac muscle fibers. Sarnoff[17] has indicated that atrial mean pressure is a satisfactory index of ventricular diastolic pressure at low and moderate levels of pressure. In addition, determination of atrial mean pressures through cardiac catheters is likely to be more reliable than determination of ventricular diastolic pressures. However, Holt[18] has demonstrated that left ventricular end-diastolic volume in the intact animal may vary widely, with little or no change in effective end-diastolic ventricular pressure. The present study, therefore, does not show that the increased stroke work of anemia is unrelated to increased diastolic ventricular volume, but only that there is no relation of stroke work to atrial transmural pressure. Alterations in heart rate may change the relation between end-diastolic ventricular pressure and volume[19] and between atrial filling pressure and stroke work.[17] Since the animals in our experiments developed a significant increase in heart rate during hypovolemia, and further increase during hypovolemic anemia, the lack of evidence of a significant relationship between stroke work and atrial transmural pressure could be due, in part, to alteration in heart rate. However, tachycardia would be expected to produce a higher end-diastolic ventricular pressure for a given ventricular volume,[19] thus leading to lower ventricular stroke work for a given filling pressure.[17] In our studies, increased ventricular stroke work without increase in filling pressure was observed, and suggested that the alteration in relationship between filling pressure and stroke work was not due to the tachycardia developed during hypovolemic anemia.

The results of the present study suggest that the Starling mechanism, as modified by Sarnoff[17] in the sense of a single curve relating stroke work to filling pressure, does not apply to the increase in cardiac stroke work in acute anemia. Sarnoff has shown that epinephrine may alter cardiac contractility and thus produce a different response curve of stroke work to filling pressure,[17] stroke work being greater for a given filling pressure during the effect of epinephrine. In view of studies suggesting that a humoral mechanism is involved in the increase of

cardiac output with acute anemia,[16] the failure of right atrial transmural pressure to rise in the presence of increased right ventricular stroke work may be due to increased cardiac contractility resulting from the elaboration of a humoral substance, such as epinephrine. The present study sheds no light on the participation of the sympathetic nervous system in the cardiac response to anemia, but this remains as a possible mechanism for future study.

The studies of Case, Berglund and Sarnoff[20] indicated that the stroke work of the dog's left ventricle decreased in response to a given filling load when the hematocrit was lowered below 24 per cent, presumably because dilation of the coronary artery was no longer able to compensate for the decreased transport of oxygen at this degree of anemia. Since hematocrits were below this value in our dogs during hypovolemic anemia, one might have expected that increased stroke work in the absence of increased filling pressure would not occur. Perhaps the vagotomies performed in the studies of Case and associates, or the urethane anesthesia limited a humoral or neurogenic response. As suggested by Holt,[18] left ventricular function may differ in the open-chest animal, as studied by Case and associates, from that in the closed-chest animal, as studied in the present experiments.

SUMMARY AND CONCLUSIONS

Circulatory dynamics of 14 dogs were studied in three periods: (1) control, (2) hypovolemia, and (3) hypovolemia with anemia. During hypovolemia, produced by bleeding 20 ml. per kilogram, there were consistent declines in right atrial transmural pressure, cardiac output, stroke volume, and right ventricular stroke work, with an increase in heart rate. Hypovolemic anemia was produced by further bleeding of 60 ml. per kilogram and simultaneous replacement of volume with dextran. The use of 6 per cent dextran in 5 per cent dextrose for exchange was shown to be associated with hyponatremia and hypocalcemia, so that the study was conducted with 6 per cent dextran in saline with added calcium, magensium, and potassium. Mean blood volume was decreased 15.5 per cent during hypovolemic anemia. The mean of hematocrits was 48.4 per cent in the control period and 16.2 per cent in the anemic period. During hypovolemic anemia, there was an increase in cardiac output, stroke volume, and right ventricular stroke work, but no increase in right atrial transmural pressure. The rise in cardiac output during hypovolemic anemia above that of the hypovolemic period was due to an increase both in stroke volume and heart rate. The increase in cardiac output over control was due, however, to an increase in heart rate, with stroke volume decreasing significantly. For this reason, right ventricular stroke work during hypovolemic anemia was not significantly increased over the control period. The results suggest that an increase in right atrial transmural pressure was not an important mechanism for increasing cardiac output or cardiac stroke work in these experiments.

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A Study of the Potentials of the Purkinje Tissue

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In a previous paper[1] we presented the electrocardiograms of the specific conducting tissue obtained in situ in the dog heart. In the discussion of those observations we referred to new possibilities for investigation opened by recording these potentials by means of a relatively easy procedure. In this paper, studies concerning the potentials of the Purkinje tissue in normal conditions and in cases of complete and incomplete bundle branch block are presented. A chart showing the distribution of these potentials in the heart is also included.

MATERIAL AND METHOD

Studies were made on 35 dogs which had an average weight of 11 kilograms. The dogs were anesthetized with pentobarbital sodium, and the chest was opened. In order to avoid wide displacement of the heart with each beat, the pericardial sac was left intact.

For the exploration of the specific conductive tissues two types of electrodes were used. One type consisted of steel needles which were approximately 45 microns in diameter at the tip and 65 microns in diameter at a distance of 0.5 mm. from the tip (Fig. 1). These were totally insulated with a plastic substance, except for the tip. Bipolar leads were recorded with a pair of these electrodes in three different situations: first, with one electrode in different segments of the conducting tissue being explored and the other nearby in the adjacent musculature, outside of the conducting system; second, in somewhat more widely separated portions of the conducting system, i.e., with one electrode in the bundle of His and the other in the right bundle branch or in the Purkinje tissue; and third, using close bipolar leads in those areas in which we thought the potentials of the Purkinje tissue could be recorded.

The other electrode used to record the potentials in these experiments was a much larger one which contained 10 bipolar leads (Fig. 2). This has been described in a previous paper.[2] Essentially it is an electrode consisting of insulated areas between carefully measured exposed intervals. Each interval is connected to a different set of marked leads, which arrangement enables us to record the potentials at different depths of the muscle where the electrode is located, without moving the electrode; in this manner one can accurately measure the depth at which the specific potentials were recorded.

Standard Lead III was used as a control in each dog.

At the end of each experiment the heart was carefully dissected "in situ," and exact measurements were made of the positions of the electrodes. This gave us an accurate localization of the sites from which the potentials of the specific tissues had been recorded.

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The potentials were recorded with a double-beam DuMont cathode-ray oscilloscope, Type 322-A, which was connected to a three-stage push-pull capacity resistance-coupled Grass preamplifier, Model P5R. Photographs of the potentials were taken with a Grass Kymograph camera, Model C4C, operated at speeds of 100 to 250 mm. per second. The range of frequencies selected was 2 kilocycles per second for the high frequencies and 7 cycles per second for the low frequencies. This allowed for partial diminution of the injury currents induced by the insertion of the electrodes.

Exploration of the Conducting Tissue in the Dog Heart.—We have already described in detail our techniques for the exploration of the conducting tissue in the dog heart.[1] In some of the tracings presented in this communication, registrations that correspond to the Purkinje potentials as well as to other structures of the conducting tissue will be observed, and for this reason it seems pertinent to review briefly our techniques for the complete exploration of the specific tissue of the dog heart "in situ."

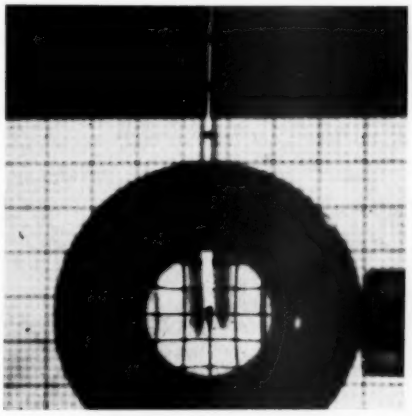

Fig. 1.—(See text.)

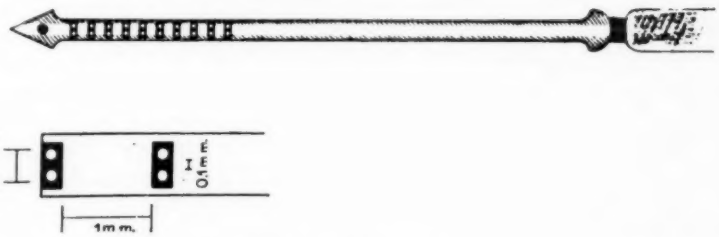

Fig. 2.—(See text.)

The A-V node is explored by placing the tip of the smaller electrode into the posteroinferior portion of the interatrial septum. This area is reached via the inferior vena cava or the surrounding portion of the free wall of the right ventricle. Special care is taken to place the needle within Koch's triangle,[3] the apices of which are located at the fossa ovalis, the coronary orifice, and the anterior septal cusp of the tricuspid valve. This placement must be very precise, otherwise no recording of the A-V node will be obtained.

It should be recalled that no definite limits exist between the A-V node and the bundle of His. In order to explore the latter it is necessary to direct the electrode toward the anterior apex of Koch's triangle, that is, toward the anterior septal cusp of the tricuspid valve. Very often we believe that one region is being explored when in reality the electrode is exploring some other region. At this point the morphology of the recorded potential should be examined on the oscilloscope. If the electrode is at the posterior portion of the triangle, close to the orifice of the coronary sinus, a slow potential from the A-V node will be seen. If the electrode is close to the anterior septal cusp of the tricuspid valve, a rapid potential characteristic of the bundle of His will be found.

In order to explore the right bundle branch the electrode is directed through the right ventricular wall to the region of the septum where this structure descends, at a point that may be located by extending a straight line from the tip of the right auricular appendage to the mid-portion of the anterior border of the septum. Transient right bundle branch block will be obtained when the electrode is correctly introduced. Should the septal surface be first accidently scratched, thus producing right bundle branch block, it will not be possible thereafter to ascertain whether the electrode is in the correct position. For this reason, the right bundle branch must be reached in a direct manner.

It is to be noted that a portion of the right branch is very superficial, practically subendocardial; therefore, the needle should never be introduced more than 2 mm. If it is introduced farther, the electrode may sometimes register the potential of the left penetrating Purkinje tissue and not that of the right bundle branch, as will be seen in the presentation of the data (Fig. 8). Even when transient right bundle branch block is clearly seen, it is always necessary to be very careful of the distance that the tip of the needle is advanced once the resistance of the septum has been felt. On occassion it was believed that the right bundle was being explored and it was found that the Purkinje potentials persisted when the next step of the experiment was carried out, viz., the production of complete right bundle branch block (Fig. 8). These potentials subsequently disappeared when the left bundle was blocked, indicating that the electrode had been introduced too deeply and, in reality, the left Purkinje potentials were being recorded (Fig. 8; see below detailed discussion of Fig. 8).

A knowledge of the different locations of the potentials of the right bundle branch and the Purkinje tissue within the P-R segment is of great importance for their final identification. For example, the potential of the right bundle branch occurs approximately 26 milliseconds after the end of the P wave in reference Lead II, and 21 milliseconds before the beginning of the QRS complex.[1] In the same reference Lead II the potential of the Purkinje tissue begins approximately 40 milliseconds after the end of the P wave and 7 milliseconds before the beginning of the QRS complex.[1]

A similar procedure is used to explore the potentials of the left bundle branch, with the production of complete left bundle branch block after control tracings have been recorded. Here again great care must be taken not to produce the block before the electrode is fixed in the bundle.

Exploration of the Purkinje Tissue.—In order to explore the Purkinje tissue, we have found that the electrode must be directed to those regions in which the presence of the Purkinje tissue has been described anatomically. These are, for the right side of the heart, the anterior papillary musculature, the apex, the trabecular zone of the right ventricular wall, and the right septal surface in its middle third.[4] In our studies, practically the entire endocardial surface of the right ventricular cavity was explored in order to be certain that no Purkinje potentials could be recorded in areas other than those mentioned. For these explorations the electrodes must be just enmeshed in the trabecular tissue. In those areas in which the potentials were recorded, the electrode was then manipulated into the adjoining cardiac mass (farther into the septum and more superficially into the free wall) in order to ascertain the depths to which the recording of the Purkinje tissue could be obtained.

The same procedure was used for the explorations of the left Purkinje tissue, which was generally found in the middle third and lower portions of the septum, at the apex of the left ventricle, and at the papillary muscles. The entire endocardial surface of the left ventricular cavity was explored.

Nomenclature Proposed for the Different Potentials of the Conducting System.—

Potential of A-V node	N-potential	Nodal
Potential of bundle of His	H-potential	His
Potential of right bundle	D-potential	Derecha-right
Potential of left bundle	I-potential	Izquierda-left
Potential of right Purkinje	Ad-potential	Arborization-right
Potential of left Purkinje	Ai-potential	Arborization-left
Potential of the muscular fibers	Bm	Bipolar of the muscle fibers

RESULTS

The Purkinje potential was usually registered as a diphasic deflection, positive-negative or negative-positive, of very short duration, which varied between 0.0028 and 0.0056 second (mean 0.0039 second).* This deflection was registered shortly before the beginning of the QRS complex of Lead III, which was usually the reference or control lead.

TABLE I

INTERVAL	NUMBER OF MEASUREMENTS	MINIMUM (SECOND)	MAXIMUM (SECOND)	MEAN (SECOND)
Ai-QRS (Lead III)				
Left septal surface	13	−0.0052	−0.0160	−0.0101
Left septal mass	11	0.0000	−0.0113	−0.0062
Free left ventricular wall	12	−0.0033	−0.0093	−0.0049
Ai-MB	19	0.0050	0.0167	0.0098
Ad-QRS (Lead III)				
Right septal surface	27	0.0000	−0.0116	−0.0056
Ad-MB				
Right septal surface	15	0.0060	0.0130	0.0094

Ai-QRS (Lead III): Interval between the left Purkinje potential and the beginning of QRS in Lead III.

Ai-MB: Interval between the left Purkinje potential and the main deflection of the close bipolar muscular lead (Bm).

Ad-QRS (Lead III): Interval between the right Purkinje potential and the beginning of QRS in Lead III.

Ad-MB: Interval between the right Purkinje potential and the main deflection of the close bipolar muscular lead (Bm).

The potential of the Purkinje fibers was registered in the middle third of the left side of the interventricular septum, both at the superficial endocardial surface and a few millimeters deeper within the left septal mass. In four experiments the intervals between the Ai potentials in the direct lead and the beginning of the QRS in Lead III were: 0.0052, 0.0044, 0.0052, and 0.0070 second. In the same experiments, we recorded with contiguous bipolar leads the intrinsic phenomenon of the muscle fibers immediately adjacent to the Purkinje tissue. The intervals between the Ai potential and the bipolar potential of these muscle fibers were: 0.005, 0.004, 0.008, and 0.007 second. These values were to be expected inasmuch as the middle third of the left septum is the region which first becomes depolarized in the ventricles. Thus, the onset of the QRS in the peripheral reference lead corresponds to the onset of the main deflection in the direct contiguous bipolar lead of the muscle fiber when the recording is obtained in the middle third of the left septum. In this area, we were able to measure the latency between the Purkinje potential (Ai) and the activation of the muscle fibers adjacent to the Purkinje tissue (Bm) (see Table I).

In Fig. 3,*A*, the upper tracing is Standard Lead III. In the lower tracing a small deflection is observed (Ai potential) which precedes the beginning of QRS in Lead III by 0.0052 second. This deflection is followed by the complex

***All measurements were made from high-speed recordings (5 mm. = 0.010 second).**

which represents the contiguous bipolar lead of the ventricular muscle (Bm) adjacent to the site of registration of the Purkinje potential. In this lead the latency from Ai to the intrinsic phenomenon (Bm) of the close bipolar lead is 0.008 second.

In Fig. 3,*B*, the upper tracing is Standard Lead III after the production of complete right bundle branch block, which may be recognized by the presence of a wide and slurred S wave. It should be noted that the potential Ai is larger than in Fig. 3,*A* and more rapidly inscribed. The contiguous bipolar tracing of the adjacent muscle is somewhat unsatisfactory, but the onset corresponds closely to that of R in Lead III. The interval from Ai to the onset of QRS in Lead III is the same as the interval from Ai to the beginning of the contiguous bipolar tracing (Bm), i.e., 0.005 second.

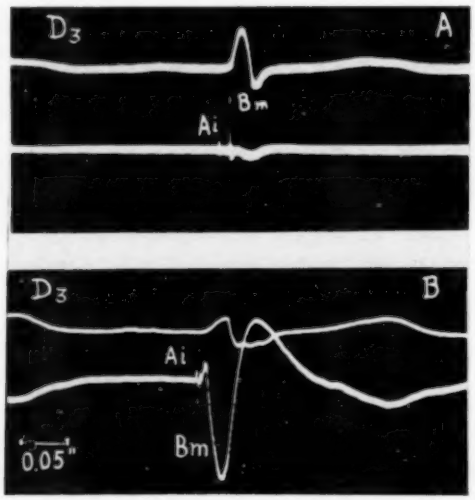

Fig. 3.—Ai and Bm potentials recorded at the middle third of the left septal surface. The upper tracing in *A* and *B* is the reference control Lead III, before and after the production of RBBB. In the lower tracing of *A* the arborization potential of the left septal surface (*Ai*) is separated from the potential of the adjacent ventricular muscle (*Bm*) by 0.008 sec. (latency).

When exploration of the Purkinje tissue of the right endocardial septal surface is being considered, it should be recalled that this region is normally activated shortly after the activation of the left endocardial septal area. It is to be expected, therefore, that the interval from Ad to the beginning of QRS in Lead III will be less than the latency between Ad and the contiguous bipolar tracing obtained at the muscle fibers adjacent to this right Purkinje tissue. In other words, by the time the activation process travels from the right Purkinje tissue (Ad) to the adjacent muscle fibers (Bm), the onset of the QRS complex has already been inscribed in Lead III, because the depolarization process has by this time invaded other areas of the left septum. This is clearly seen in Fig. 7,*B*, which will be described later.

The Purkinje Potentials of the Left Septal Mass.—These potentials were registered in the anterior, middle, and posterior portions of the middle third of

the left septal mass and at different depths up to a level of 5 mm. from the left septal surface. They were also registered in the lower third of the septum but not in the upper third. It is difficult to explore the high middle portions of the left septal surface because left bundle branch block is produced quite easily in that area, and this causes a delay in the inscription of Ai, which becomes superimposed on the QRS complex, making its recognition quite difficult (see below).

It was observed that the Ai potentials in the tracings from the left septal surface were separated farther from the onset of the QRS in the reference Lead III than in the other sites explored in the left ventricle. The following intervals, measured in one experiment (Fig. 4), are those that separate the Ai potential from the QRS in Lead III: in the superficial endocardium (*1*) the value was 0.0130 second; at a depth of 1.6 mm. from the left septal surface (*2*) the value was the same 0.0130 second; at 3 mm. from the septal surface (*3*) it was 0.0083 second, and at a depth of 4.8 mm. (*4*) the interval was 0.0030 second (Fig. 4).

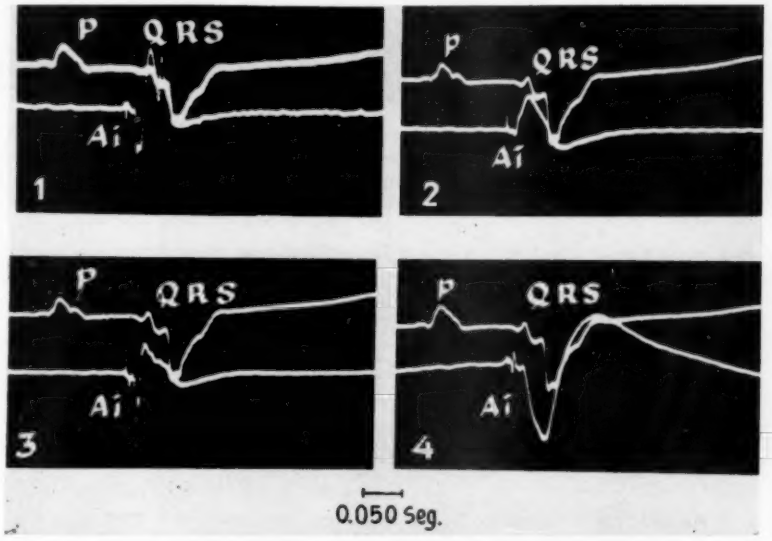

Fig. 4.—Intervals between the Ai potential and the beginning of QRS in Lead III, in tracings obtained at various depths in the left septal mass. In *1* (left septal surface) the interval is 0.0130 sec.; in *2* (at a depth of 1.6 mm.) the value is the same as that in *1*; in *3* (at a depth of 3 mm.) the interval is 0.0083 sec.; and in *4* (at a depth of 4.8 mm.) the interval is 0.0030 sec. At depths greater than this the arborization potentials were not registered. The upper tracings are the control reference Lead III, which shows an important degree of RBBB.

At depths greater than this we could not register the arborization potentials. Thus, the Ai potential was inscribed later (closer to the QRS) as the exploring electrode entered deeper into the left septal mass. It should be noted that reference Lead III in Fig. 4 shows right bundle branch block, but as we shall show later in greater detail, the Purkinje potentials of the left septal areas are not affected in this condition.

The results, therefore, are quite similar when the activation is normal, as in the experiment of Fig. 5: in *1* the recording was at the middle third of the left septal surface, and Ai was inscribed 0.052 second before the onset of the QRS

complex in reference Lead III; in *2*, at a depth of 1.6 mm. from the septal surface the Ai was inscribed 0.0044 second before the reference QRS; in 3, at a depth of 3 mm. the Ai was not registered; in *4*, *5*, and *6*, recorded in the same positions as *1*, *2*, and *3*, after the production of complete right bundle branch block, the same intervals and conditions persisted.

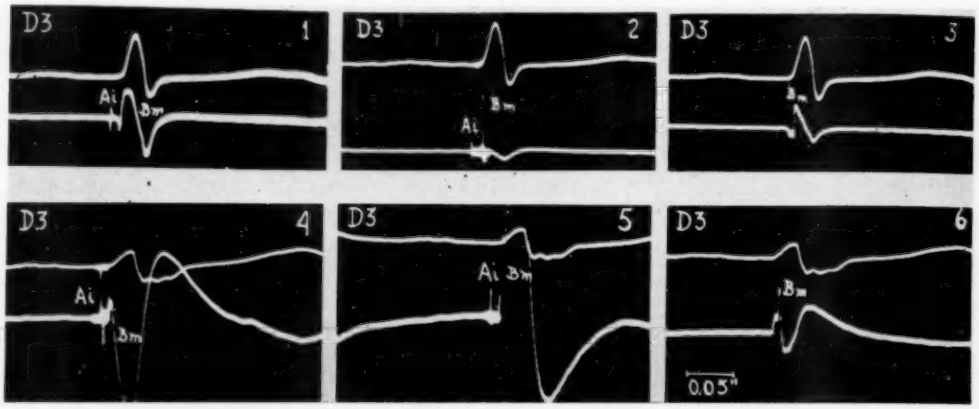

Fig. 5.—Intervals between Ai and Bm at different depths in the left septal mass, before (*1,2,3*) and after (*4,5,6*) RBBB. The intervals of corresponding positions did not change. In all of the records the upper tracing is Lead III.

In Fig. 6 the lower tracings show registrations of the potentials of the bundle of His and of the left Purkinje tissue. The upper tracings represent reference Lead III, with complete right bundle branch block evidenced by the wide and slurred S wave. As we have mentioned in the methodology, one electrode of a distant bipolar lead was placed in the bundle of His and the other electrode was placed at various depths from the endocardium at the middle third of the left septal surface. In *1* of Fig. 6 the electrode was at the endocardial surface, and the interval between H and Ai is 0.0264 second; in *2*, the septal electrode was recording at a depth of 1.6 mm., and the interval was 0.0268 second; in *3*, the depth of the recording was at 3 mm., and the interval was 0.0276 second. Therefore, the interval between the potential of His (H) and the Purkinje potential (Ai) increased (or Ai became closer to the QRS) as the electrode was placed deeper into the septal mass. These findings are in agreement with those shown in Fig. 4.

The Purkinje Potentials of the Right Septal Mass.—These potentials were recorded from the anterior and middle portions of the middle third of the right septal mass and from the base of the anterior papillary muscle. This mass is much thinner in these regions than in the corresponding portions of the left septum. For this reason, only two recordings were obtained: one from the superficial endocardium and the other at a depth that varied from 1 to 3 mm.

In Fig. 7,*A*, the lower tracing shows an Ad potential which is inscribed 0.010 second before the beginning of QRS in reference Lead III (upper tracing). This recording was made in the endocardium of the right ventricular cavity at the base of the anterior papillary muscle. Fig. 7,*B* shows a similar tracing with

reversed polarity (the leads had been accidentally changed) which was obtained in the mass of the anterior papillary muscle at a depth of 1 mm. The electrical phenomenon of the arborization now has its onset 0.008 second before the beginning of the QRS in Lead III. In these tracings, one can also observe the period of latency between the activation of the Purkinje tissue (Ad) and that of the adjacent muscle fibers (Bm), which was 0.013 second in both tracings. Similar values for these intervals were commonly found in other experiments in which the potentials of the right Purkinje tissue were explored. As we mentioned previously, in Fig. 7,*B* the interval from Ad to the beginning of QRS in Lead III is less than the latency between Ad and the contiguous bipolar tracing obtained at the muscle fibers adjacent to this right Purkinje tissue (see above).

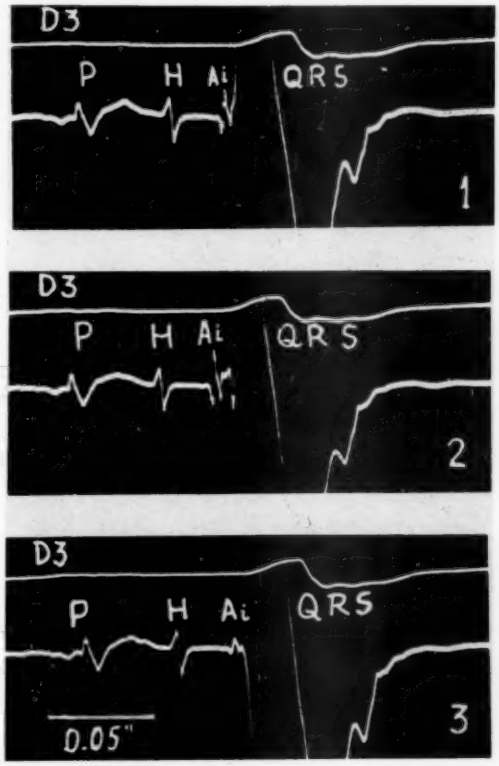

Fig. 6.—Intervals between H (potentials of the bundle of His) and Ai (Purkinje potentials) recorded at different depths in the left septal mass. In all of the records the upper tracing is the control reference Lead III.

EXPERIMENTAL OBSERVATIONS INDICATING THAT THESE POTENTIALS ARE DERIVED FROM THE PURKINJE TISSUE

I. We have recorded a clearly defined deflection before the onset of the QRS complex in the control lead. The interval that separates this deflection from the beginning of the QRS varies from 0.0052 up to 0.016 second. There is also an isoelectric line between this deflection and the beginning of the ventricular complex in most of the direct bipolar leads.

II. The potentials which we believe correspond to those of the Purkinje tissue can be easily recorded in those areas (Fig. 14) in which Purkinje tissue has been described anatomically or histologically. Furthermore, we could not find these deflections in the regions at the base of the heart and in other areas in which the Purkinje tissue has not been described. The sites at which these deflections could be most easily recorded were those at which the first ramifications of the Purkinje tissue have been histologically described: for the left ventricle, in the middle third of the interventricular septum, and for the right ventricle, near the anterior papillary muscle of the right septal surface. These observations are in accordance with the original descriptions of Purkinje[5] and Lewis,[4] and with those of Pruitt and Essex.[17]

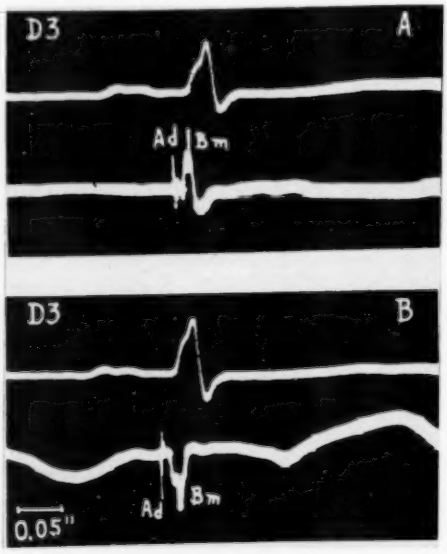

Fig. 7.—The Purkinje potentials of the right septal mass. In *A* the lower tracing was recorded at the endocardial surface near the anterior papillary muscle, and the interval between Ad and QRS in reference Lead III (*upper tracing*) was 0.010 sec. In *B* the same interval is 0.008 sec. when the tracing was obtained in the mass of the anterior papillary muscle at a depth of 1 mm.

III. As we explored the interventricular septum, and our electrode went deeper into the septal mass, that is, farther away from the endocardial surface, we were able to record these deflections to a depth of only 5 mm. in the left septal mass and 2.5 mm. in the right septal mass. We believe that this is a highly significant observation and controverts two possible criticisms. The first is that this deflection could be an artefact. But if it is recorded at the depth of 1 or 2 mm., why does it then disappear at a depth of 3 or 5 mm.? The second possible criticism is that this deflection in reality corresponds to a component of the QRS and does not represent an independent potential. As we have already pointed out, a definite isoelectric line is seen between the potential and the QRS. Furthermore, in the light of such an objection, how can the disappearance of the potential be explained as the electrode goes slightly deeper into the septal mass?

IV. The short duration of this deflection (average, 0.0039 second) is in agreement with the rapid rising limb that has been described in the monophasic action potential of the isolated Purkinje tissue obtained with microelectrodes.[6]

Of course, these are all primarily indirect proofs. We have attempted to obtain more direct evidence to support our views.

V. We should expect that the existence of a complete right bundle branch block would obscure the deflection from the right ventricle if it is indeed the Ad potential, whereas the deflection representing the left Purkinje tissue, Ai, would remain with this type of block. On the other hand, complete left bundle branch block would obscure the Ai potential, whereas the Ad potential would be unaffected.

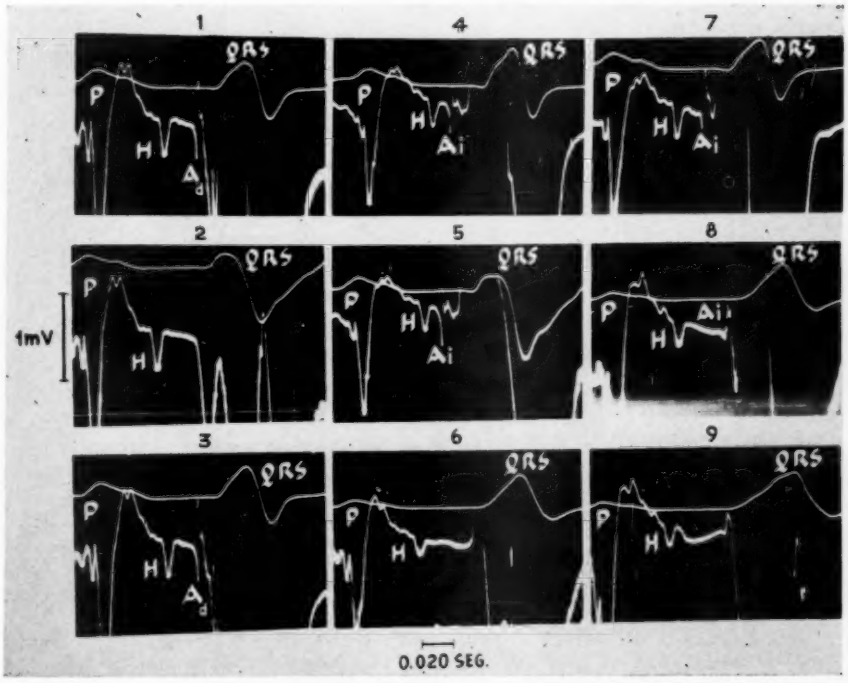

Fig. 8.—Disappearance of the Ad potential with RBBB, and of the Ai potential with LBBB (see text).

With these considerations in mind let us carefully examine Fig. 8. In *1* of Fig. 8 the upper tracing corresponds to control Lead III, and in the lower tracing the potentials H and Ad are clearly seen. In *2*, a right bundle branch block has been produced (wide and slurred S wave in Lead III). This caused the disappearance of the Ad potential, and only the H potential remained. In *3*, the right bundle branch has recovered and once again the Ad potential is recorded with the same chronology as in the original tracing. In the same experiment the deflection Ai—potential of the left endocardial Purkinje tissue—was also recorded, as seen in *4*. This deflection did not change after the production of the right bundle branch block (*5*). With the production of incomplete left bundle branch block the Ai disappeared (*6*) or its inscription was retarded (*8*), and with com-

plete left bundle branch block it also disappeared, as would be expected (*9*). Part *7* of Fig. 8 is a control tracing obtained between incomplete and complete left bundle branch block. This figure was mentioned in the section on material and method (see above). It was believed that the Ai potential of tracings *4* and *5* of Fig. 8 corresponded to the potential of the right bundle branch. After incomplete left bundle branch block was produced (*6* of Fig. 8), the diphasic potential disappeared, thus forcing us to the conclusion that we were exploring the left penetrating Purkinje tissue, as was later confirmed when the electrode was found to lie 8 mm. from the right endocardial surface, close to the left septal surface.

In another experiment we provoked incomplete and complete atrioventricular block in a further effort to find positive or negative evidence that we were indeed registering the potential of the Purkinje tissue. In *1* of Fig. 9 the upper tracing is control Lead III, with a first-degree A-V block and complete right bundle branch block (wide slurred S wave). In the lower tracing the H and Ai potentials are clearly seen. We must keep in mind that it is always possible to record Ai in right bundle branch block, since we are recording this deflection from the left endocardium, the activation of which is not delayed. In *2* of Fig. 9 the P-R interval increases, but the time between H and Ai remains the same as in *1*. After the registrations of tracing *2*, complete A-V block was produced, and in *3*, only the P wave is seen, followed in *4* (this is a continuous tracing) by a QRS complex which is unrelated to the previous P wave. The H and Ai deflections have disappeared, even though the ventricular rhythm appears to be originating from the left ventricle because of the morphology of the QRS complex in Lead III. The same patterns are shown in *5* and *6* of Fig. 9, that is, complete A-V block with no H or Ai potentials recorded. In *7* of Fig. 9 the complete block has undergone transition to first-degree A-V block, with marked prolongation of the P-R interval, and once again H and Ai are registered with the same interval between them as in the original control.

VI. In order to obtain more direct proof, we injected 2 Gm. of procaine amide intravenously after having recorded the Ai potential in the middle third of the left septal mass (1.6 mm. from the left septal surface). With this procedure we observed (Fig. 10) further separation of the Ai potential from the beginning of QRS in Lead III, as well as from the direct bipolar lead (Bm).

In the upper control tracing of Fig. 10, Ai precedes the QRS complex of Lead III by 0.0148 second. The other tracings of Fig. 10 were obtained during a consecutive 10-minute period after the first changes were recognized on the oscilloscope. As a result of the action of the drug, the time between Ai and the beginning of QRS in Lead III increased progressively from 0.0148 to 0.0220 second, 0.0308, 0.0344, up to 0.0372 second. The latency between Ai and the main deflection of the close bipolar lead (Bm) also increased in a parallel fashion, from 0.0300 to 0.0988 second. This experiment suggests, as we previously postulated,[7] that procaine amide produces a block or delay in the passage of the activation wave from the Purkinje tissue to the adjacent muscle fibers. Also, it clearly supports the concept that the Ai potential originates in myocardial structures (Purkinje tissue) different from the structures which produce the QRS or Bm potentials (myocardial muscle fibers).

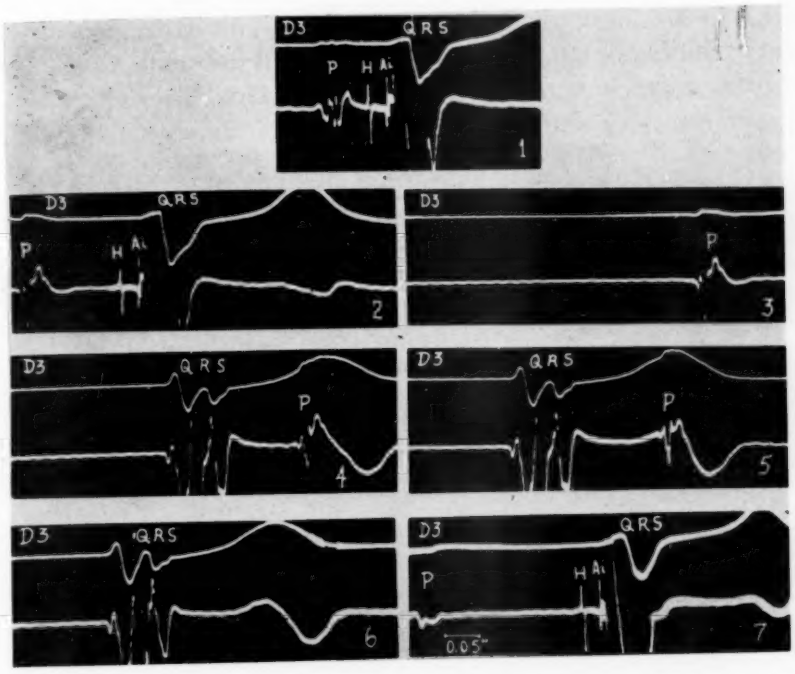

Fig. 9.—Disappearance of the H and Ai potentials with complete A-V block (see text).

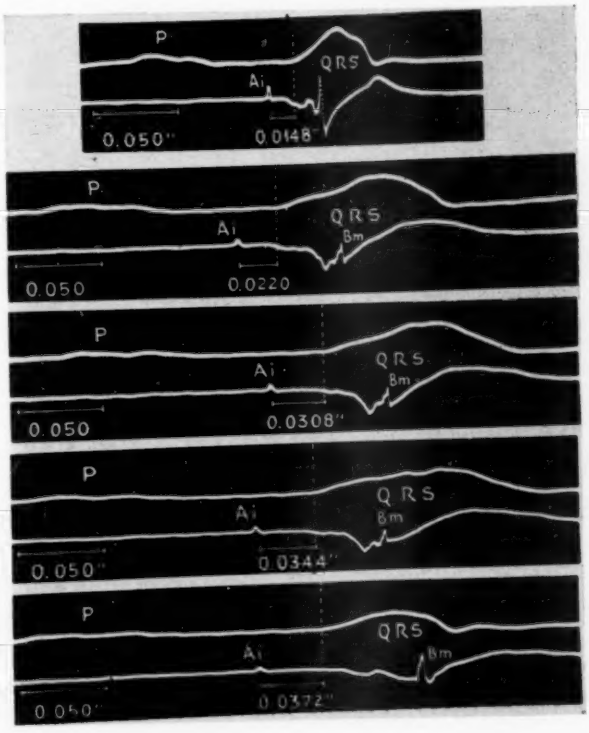

Fig. 10.—Progressive separation of the Ai potential from the beginning of QRS, due to the action of procaine amide.

Fig. 11 shows the findings in a similar experiment. The interval between Ai and the beginning of QRS in Lead III increased from 0.0142 to 0.0552 second, because of the action of the procaine amide.

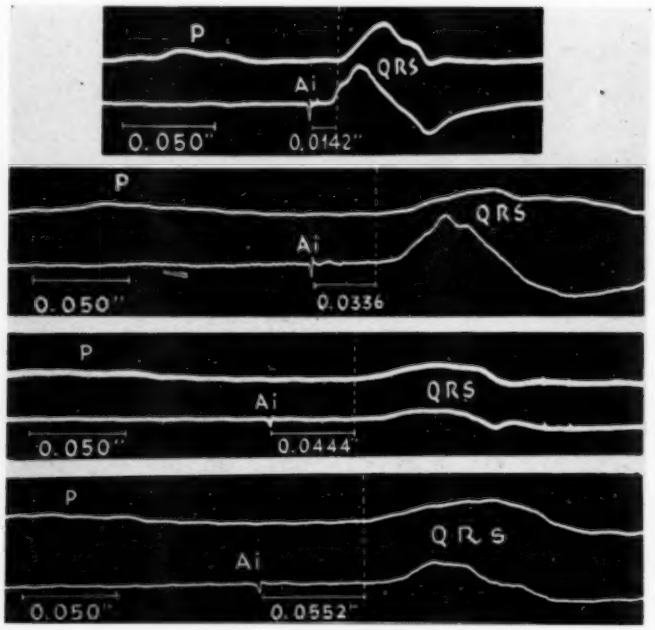

Fig. 11.—Progressive separation of the Ai potential from the beginning of QRS, due to the action of procaine amide.

THE PURKINJE POTENTIALS IN INCOMPLETE AND COMPLETE BUNDLE BRANCH BLOCK

Fig. 12 shows the right Purkinje potential (Ad) obtained on the endocardial surface at the base of the right anterior papillary muscle in normal conditions and with different degrees of right bundle branch block. In the lower tracing of *1* of Fig. 12 the H potential is followed at 0.021 second by a rapid deflection, the Ad potential. Reference Lead III is recorded in the upper tracing. In *2* of Fig. 12 the reference lead shows a slight degree of right bundle branch block, which may be recognized by a widened QRS, decrease in the height of the R wave, and slurring of the S wave. The Ad potential is still present, but the interval between H and Ad is now 0.031 second. In *3* and *4* of Fig. 12 the Ad potential is well defined, but the interval has increased to 0.033 and 0.038 second, respectively. Now the Ad potential is beginning to be superimposed on the adjacent QRS complex. Observe that the degree of right bundle branch block increases progressively from *2* onward, until complete right bundle branch block is recorded in *5*. At this point the Ad potential is not recognizable in the P-R segment. Nevertheless, a rapid diphasic potential of short duration can be observed in the direct lead (lower tracing in *5* of Fig. 12), synchronous with the nadir of the S wave in Lead III (upper tracing in *5*). This is indicated as Ad with a question mark, since it was felt that this may or may not have been the Ad potential. The interval between H and the assumed Ad potential (*Ad?* in Fig. 12) is 0.083 second.

The experiment shown in Fig. 13 registers the relationship between the H and Ai (left Purkinje potential) before (*1*) and after (*2*) the production of a complete left bundle branch block. The Ai potential was recorded at the middle portion of the left septal surface. In *1*, the Ai of the direct lead (lower tracing) precedes the inscription of the QRS Lead III (upper tracing). The interval between H and Ai in these control conditions is 0.020 second. In *2*, the Ai complex is not seen preceding the QRS, but in the ventricular complex of the direct bipolar lead a rapid short deflection that may or may not correspond to the Ai potential is recognized. The delayed inscription of this deflection would be expected, a priori, in view of the fact that left bundle branch block always delays the activation of this portion of the left septal mass. An examination of *1* and *2* alone is not sufficient to make us conclude that this deflection is indeed the Ai potential; for this reason, it is also indicated with a question mark. However, a

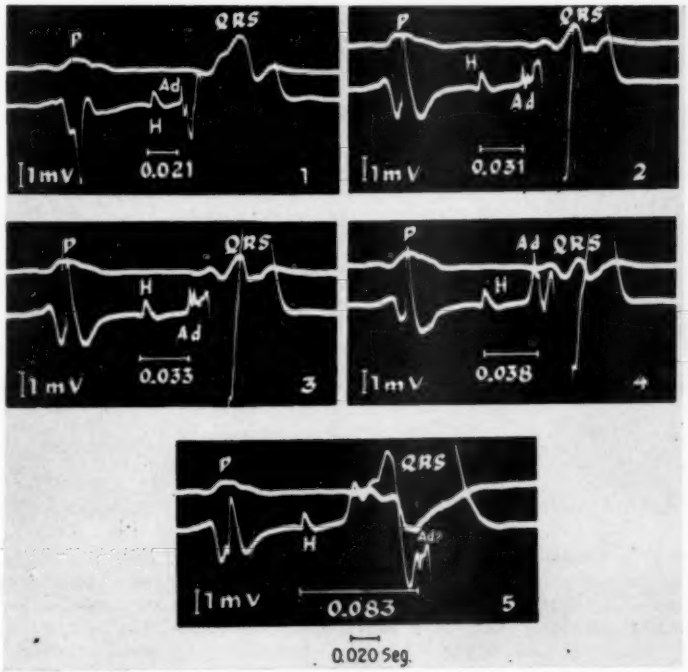

Fig. 12.—Progressive delay of the inscription of the Ad potential as the degree of RBBB is increasing. When the block is complete, Ad disappears from the P-R segment and is inscribed superimposed on the QRS complex.

careful examination of the tracings recorded immediately after the second one, i.e., *3* through *10* of Fig. 13, shows that the rapid deflection recognized in the distant bipolar lead approaches the H potential step by step, in proportion to the diminution of the degree of left bundle branch block, until it reaches again the same interval and configuration as in the control conditions. With an advanced degree of left bundle branch block the interval between H and Ai was 0.099 second. As the left bundle branch block diminished, the interval became 0.070, 0.062, 0.053, 0.040, 0.036, and 0.033 second, respectively, until finally it was

registered with an interval of 0.020 second, as in the control tracing. This evolution leads us to conclude that this deflection is the Ai potential that was recorded in the original tracings.

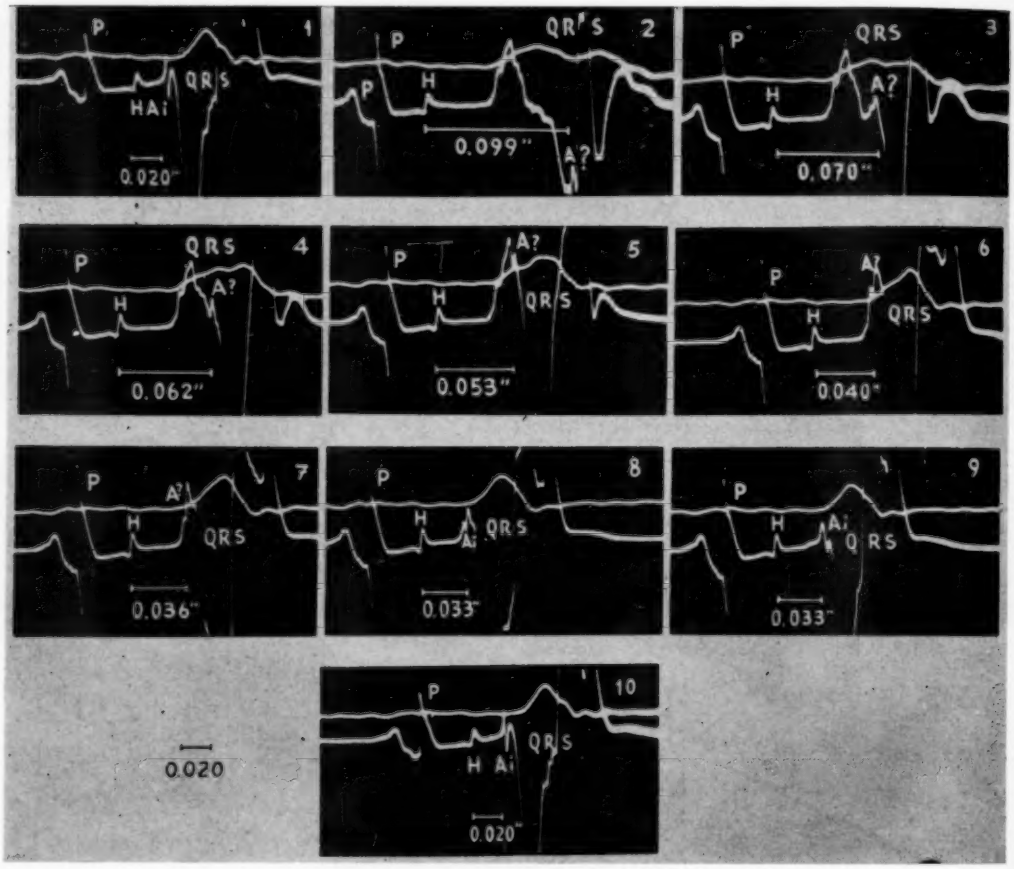

Fig. 13.—The Ai potential with LBBB. When the block is complete, the Ai potential is superimposed on the QRS complex, and the interval between H and Ai increases importantly. As the degree of block diminishes, the H-Ai interval is proportionally reduced and the Ai deflection becomes earlier in its inscription until it reaches its normal situation in the P-R segment.

DISCUSSION

A. *The Purkinje Tissue in Relation to the Normal Activation Process of the Heart.*—

1. *Activation of the interventricular septum:* It is already known that the first region to become activated in the interventricular septum is at the middle third of the left septal surface where the left branch first ramifies. In this region we registered the earliest potentials of the Purkinje fibers, before the beginning of QRS in the reference lead. The mean value of the interval between Ai and QRS in Lead III is 0.0101 second, and sometimes this interval may be as long as 0.0160 second (see Table I). These figures are greater than those between Ad and QRS in Lead III when recordings are made from the right septal surface.

The greatest interval between Ad and QRS in Lead III was 0.0116 second, and the mean value was 0.0056 second. These values can be explained if one assumes that the stimulus of activation arrives earlier to the left Purkinje fibers (Ai) than to the right ones (Ad).

On the other hand, the latency period (Purkinje tissue–adjacent muscle fibers) is similar for both sides of the heart, that is, the values of the interval Ai-Bm are of the same order as those of Ad-Bm. These findings suggest that the difference in activation time between the right and the left septal surfaces does not occur at the level of the Purkinje fibers but more proximal, within the branches. In a previous paper[1] we presented evidence to show that the trunks of both branches are activated simultaneously; therefore, the distribution of the first ramifications, which are higher on the left branch than on the right, is an important anatomic fact which accounts for the temporal differences.

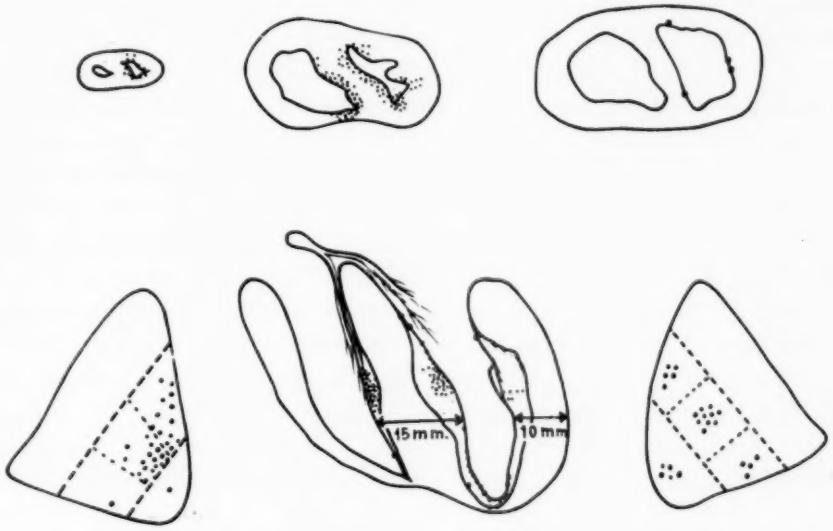

Fig. 14.—Mapping of the distribution of the Purkinje potentials in the dog heart. The areas in which there is profuseness of Purkinje tissue, as registered electrically, are: the middle third of the left septal surface, the anterior portions of the middle third of the right septal surface, the middle portions of the right and left septal masses. The regions in which there is lesser density of Purkinje tissue, as registered electrically, are: the apex of the left ventricle, the trabecular zone of the right ventricle, and the subendocardial middle portions of the free left ventricular wall. At the base of the heart the Purkinje potentials were rarely registered, which suggests that the Purkinje fibers are scarce or absent.

The potentials of the Purkinje fibers were registered up to a depth of 5 mm. in the middle third of the left septal mass. These findings are in agreement with the rapid normal activation that we have described in this area and suggest that a profuseness of Purkinje tissue exists here.

The absence of Purkinje potentials at the base of the interventricular septal mass (Fig. 14) readily explains earlier findings, that is, the relatively slow and late activation in these regions. This again suggests that the arrival of the activation wave in the high portions is by propagation through nonspecific muscle fibers, as we proposed several years ago.[7,8]

2. *Activation of the free left ventricular wall:* In previous papers,[9,10] we reported that the inner portions of the free left ventricular wall are rapidly and almost simultaneously activated. Other authors have confirmed these observations.[11,12] This is in accordance with the fact that in this series of experiments the Purkinje potentials were commonly recorded in the endocardium of the free left ventricular wall. Of further interest is the fact that these potentials could be recorded to a depth of 4 mm. at the middle third of the lateral portion of the left free wall. The potentials could not be recorded in the basal regions of this wall. In these sites there is slow and late activation quite similar to that found at the base of the intraventricular septum. Thus, the last zones to become activated in the free wall of the left ventricle are the high lateral and the posterior zones. In these areas the Purkinje fibers are anatomically scarce or absent, and electrical exploration for the specific potentials is negative.

3. *Free right ventricular wall:* The Purkinje potentials were registered only in the trabecular zone, close to the interventricular septum, and not in the rest of the free right ventricular wall. The activation wave in these remaining portions is probably transmitted through nonspecific muscle fibers; thus, the positivity recorded at the right epicardial surface must be related to the slow conduction as well as to the thickness of the wall, which is greater in the basal regions. From this point of view, the morphologies rS at the trabecular zone, RS at the middle portions, and Rs at the basal regions of the right epicardial surface of the dog heart are easily explained. According to the findings of Barbato and co-workers,[18] complexes of the rS type are registered, in the human heart, in most of the areas of the epicardium of the free right ventricular wall. We believe, therefore, that the right Purkinje network ramifies more extensively in the human than in the dog heart. To confirm this hypothesis, the exploration of the right Purkinje potentials should be made in patients during heart operations.

B. *The Potentials of the Purkinje Tissue in Relation to the Activation Process in Bundle Branch Block.*—We have observed that a complete right bundle branch block causes the disappearance of the Ad potential from the P-R interval, whereas the Ai remains; and complete left bundle branch block causes the disappearance of the Ai potentials from the P-R interval but the Ad deflection is unaffected.

In incomplete right bundle branch block the Ad potential is progressively delayed according to the degree of the block, and when complete block occurs, the Ad potential is inscribed superimposed on the QRS complex. In regard to the Ai potential the same phenomena appear in cases of incomplete left bundle branch block. It is very important to emphasize that the potentials Ai and Ad were delayed in accordance with the degree of block in all experiments, without any exceptions. This suggests to us that the muscular tissue of the trunks of the branches forms a syncytium rather than separated channels. Were it not so, the experiments would have varied results, since by chance the same "channels" could not be blocked each time, and therefore, the Ad potentials for right bundle branch block, as well as the Ai for left bundle branch block, would have been delayed only in some and not in every experiment that was performed. For this reason, the existence of several channels through the branches before they start to ramify is, in our opinion, less likely.

In those experiments in which a complete right bundle branch block was produced the Ai deflection recorded up to a depth of 5 mm. was inscribed normally before the beginning of QRS in the reference lead. At the same time the Ad potential was markedly delayed and its inscription was superimposed on the QRS complex (Bm). The time difference between Ai (unblocked side) and Ad (blocked side) was 0.063 second. In the cases of left bundle branch block, the Ad was normal in time and the Ai was delayed. The time difference in this case was 0.072 second. These delays in the conduction across the septum suggest again the existence of a physiologic septal barrier, as proposed by us in previous papers.[13-16]

SUMMARY

(1) The Purkinje potentials were registered in different regions of the interventricular septum and the free ventricular walls in the dog heart. (2) A mapping of the distribution of these potentials is presented. (3) Experimental proof that the deflections recorded represent the potentials of the Purkinje tissue is given. (4) The behavior of these potentials in cases of complete and incomplete bundle branch block, as well as with different degrees of A-V block, was studied. A progressively delayed inscription of these potentials was found in respect to the potentials of the bundle of His as well as a progressive approach to the beginning of QRS in Lead III in the blocked side. (5) The behavior of the Purkinje potentials recorded at the interventricular septum after complete bundle branch block speaks in favor of the existence of a physiologic barrier which separates the left and right septal masses.

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Some Fundamental Relationships Between Oscillographic and Spectrographic Phonocardiograms

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Heart sounds have been recorded in oscillographic form since Einthoven originally used the capillary electrometer for this purpose.[1] In the intervening years the techniques of conventional phonocardiographic registration have improved progressively, and it appears at the present time that the oscillographic phonocardiograph is rapidly gaining acceptance as a valuable clinical diagnostic tool.

During the past 12 years or so there has also been considerable active interest in the vibrational frequency content of various types of heart sounds. In some laboratories this interest has taken the form of broad band-pass filtration of heart sounds.[2,3] In other laboratories a given set of heart sounds, recorded on magnetic tape, is played back repetitively through a narrow band-pass filter. The center frequency of the filter is shifted a given step with each replay, and the entire spectrum of frequencies thus derived is recorded.[4-7] In at least one other laboratory the frequency components have been determined from oscillographic tracings by means of lengthy mathematical calculations.[8,9]

In the language of the physical scientist, the conventional or oscillographic phonocardiogram is a representation of a biophysical phenomenon in the time-domain. The spectrographic display of the same phenomenon constitutes representation in the frequency-domain. It would seem a priori that some sort of fundamental and definitive relationship must exist between these two modes of registration of heart sounds.

Such a relationship does indeed exist. However, in searching through the clinical, and closely allied, literature we have failed to discover any reference to the relationship in question. Therefore, it is our intent in the present communication to introduce this powerful unifying concept into the clinical litera-

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ture, to illustrate its significance by means of a few simple examples, and to comment briefly upon some of its potential applications to the problem of registration and analysis of heart sounds.

THEORETICAL CONSIDERATIONS

The principles of Fourier analysis are reasonably well known, and are applicable to sustained, periodic vibrations such as musical heart murmurs. Fourier analysis is customarily performed on a single cycle of the periodic function, and represents the function as the sum of a series of sinusoidal oscillations of given frequency, amplitude, and phase.[10] The frequency of the fundamental component is identical to the frequency of the analyzed vibratory function; the frequencies of the other components are exact multiples of the fundamental frequency. An oscillogram of the total function would constitute a time-domain display of the function; conversely, a graph which indicated the frequency, phase, and amplitude of each of the respective sinusoidal components would constitute a frequency-spectrum, or frequency-domain, display of the same vibrations. The character of the function in either domain is deducible from a knowledge of its characteristics in the other domain.

The essential nature of Fourier analysis limits its use in the physics of sound to musical tones. Presumably, then, the method is not generally applicable to heart sounds because most of them are nonmusical. However, there is an extension of the Fourier method which is applicable to numerous types of functions, including any burst of sound vibrations which could conceivably be generated by the heart. Conceptually, in the application of this extension of the theorem to a given burst of sound vibrations, the wave train is treated as an isolated phenomenon in the time-domain. The entire burst of sound, together with the zero-deflection state which is assumed to exist prior to and after the sound, is treated mathematically as a 1-cycle periodic function of infinitely great cycle length. This maneuver, which in some respects is simply a mathematical artifice, transforms the vibrations from the time-domain to the frequency-domain in a manner which is entirely analogous to the application of Fourier analysis to periodic functions of finite cycle length.[11]

A burst of vibrations which can be expressed in a given mathematical form in the time-domain will have another, but implicitly related, mathematical form in the frequency-domain. The two mathematical expressions in question are Fourier transform pairs. The application of Fourier transform pair theory to a few simple types of oscillations is illustrated in the following section.

FREQUENCY SPECTRA OF SIMPLE OSCILLATIONS

The n-Cycle Burst of Simple Harmonic Oscillations.—A wave train of sinusoidal vibrations having a frequency, f_0, and a duration of n cycles is expressed by the equation

$$f(t) = \left[(-1)^n \sin \omega_0 t \right]_{t = -\pi n/\omega_0}^{t = \pi n/\omega_0} \tag{1}$$

where $\omega_0 = 2\pi f_0$, and f(t) indicates "function of time." Equation 1 is a time-domain expression. The associated frequency-domain expression is determined by evaluating the integral

$$g(\omega) = \int_{-\infty}^{\infty} f(t)\ e^{-i\omega t}\, dt \tag{2}$$

where g(ω) indicates "function of frequency," e is the base of natural logarithms, i is $\sqrt{-1}$, and ω is 2π times the frequency, f. In the specific case under consideration here, Equation 2 becomes

$$g(\omega) = (-1)^n \int_{-\pi n/\omega_0}^{\pi n/\omega_0} e^{-i\omega t} \sin\ \omega_0 t\ dt \tag{3}$$

the solution of which is

$$g(\omega) = \frac{2i}{\omega_0}\ \frac{\sin\ \pi n\alpha}{1 - \alpha^2} \tag{4}$$

where $\alpha = f/f_0 = \omega/\omega_0$.

Upon initial inspection, the physical significance of g(ω) in Equation 4 may not be entirely clear because it is an imaginary function, and it implicitly contains negative as well as positive frequency terms. Suffice it to say at this juncture that these two confusing items may be discarded for the time being, and that upon so doing *the amplitude of g(ω) in Equation 4 represents directly the frequency spectrum of the sinusoidal oscillations.*

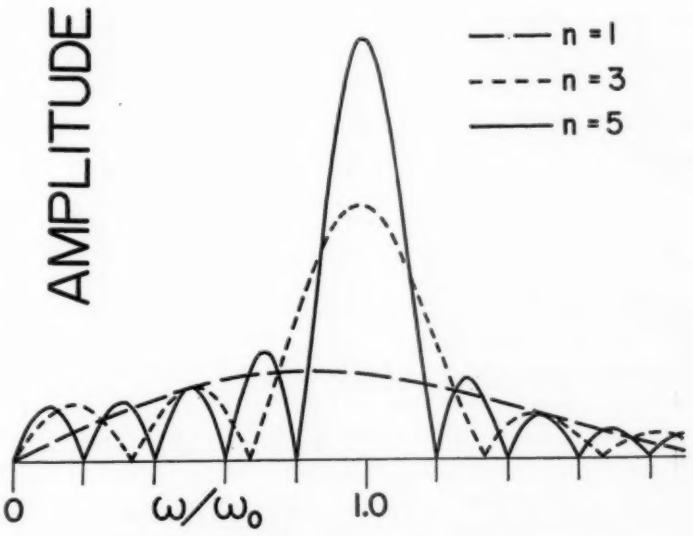

Fig. 1.—Frequency spectra of 1-, 3-, and 5-cycle bursts of sinusoidal oscillations which have an angular frequency of ω_0. The angular frequency of the spectrum components is ω. For a given value of ω_0, the limiting envelope of the frequency spectrum is identical for all n-cycle and (n + ½)-cycle bursts except in the peak frequency band. The magnitude of the ω_0 component is directly proportional to n or n + ½.

We employed Equation 4 in the case of a 1-, 3-, and 5-cycle burst of simple harmonic vibrations, and the frequency spectra thus determined are shown in Fig. 1. The following comments on the three frequency spectra appear to be pertinent: (a) The spectra are continuous, with all frequencies being represented except at the nodes of zero amplitude, and at infinitely rapid frequencies. (b) The limiting envelope of all of the spectrum patterns is identical, except that it is without limit at the frequency, ω_0, where (c) the amplitude of the ω_0 component is directly proportional to the number of cycles in the time-domain oscillations. (d) Although the oscillations are actually short time-segments of a simple musical tone, the frequency spectra suggest that they would be perceived as noise. In addition to the above comments, Equation 4 indicates further that the relative amplitude of the spectrum components is inversely proportional to the frequency of the harmonic oscillations. One significant aspect of this last fact, which will be pursued further in the discussion section of this report, is that small, superimposed notches and slurs would tend to produce only minor alterations in the basic spectrographic pattern.

In the case of the $(n + \frac{1}{2})$-cycle burst of oscillations the frequency-spectrum expression is of the form

$$g(\omega) = \frac{\cdot}{\omega_0} \quad \frac{\cos \pi \, (n + \frac{1}{2}) \, \alpha}{1 - \alpha^2} \tag{5}$$

This function has the same limiting envelope as does the n-cycle case; and the peak frequency amplitude is inversely proportional to $n + \frac{1}{2}$, as compared to the n-cycle case where the peak amplitude is inversely proportional to n.

Wave Trains With Gradual Onset and Termination.—We suspected that the abrupt onset and offset of the sonic energy bursts were largely responsible for the exceptionally wide range of their frequency spectra (cf. Fig. 1). We tested this idea by determining the frequency spectra of a 4-cycle burst before and after modifying the abruptness of onset and offset. Fig. 2,*A* illustrates the unmodified burst of oscillations. The mathematical expression of the function is given by Equation 1. Fig. 2,*B* is the same oscillatory function, modified by the two superimposed functions:

$$f_1(t) = -\omega_0 \, (t + T) \, e^{-1.5 \, \omega_0 \, (t + T)} \tag{6}$$

$$f_2(t) = -\omega_0 \, (t - T) \, e^{1.5 \, \omega_0 \, (t - T)} \tag{7}$$

In both of the equations, $T = 4\pi/\omega_0$, the period of two oscillations. In Equation 6, $t \geq -T$; and in Equation 7, $t \leq T$. As is evident in Fig. 2,*B*, the effect of the superimposed functions, $f_1(t)$ and $f_2(t)$, is to produce a zero slope at the beginning and end of the wave train.

Wave train, Fig. 2,*C*, is an amplitude modulated form of Fig. 2,*A*, and may be expressed as

$$f(t) = \left[(\sin \omega_0 t) \, (\cos \frac{\omega_0}{8} t) \right]_{t = -4\pi/\omega_0}^{t = 4\pi/\omega_0} \tag{8}$$

The onset and offset in this case is considerably more gradual than in Fig. 2,*B*.

The frequency spectra of these three oscillatory events are shown as patterns *A*, *B*, and *C*, respectively, of Fig. 3. These patterns confirm that the high- and low-frequency content of the spectrograms is related to the abruptness of onset and offset. Reducing the abruptness of onset and offset tends to augment the amplitude and breadth of the "carrier frequency" band of the spectrogram.

Frequency Spectra of So-Called Memory Functions.—In the preceding sections we have confined our attentions to the frequency spectra of rather arbitrary, and somewhat synthetic, oscillations. We now turn to a class of vibrations which commonly occur in nature, and which, according to Huggins' concept of sound production,[12,13] could be employed to represent heart sounds.

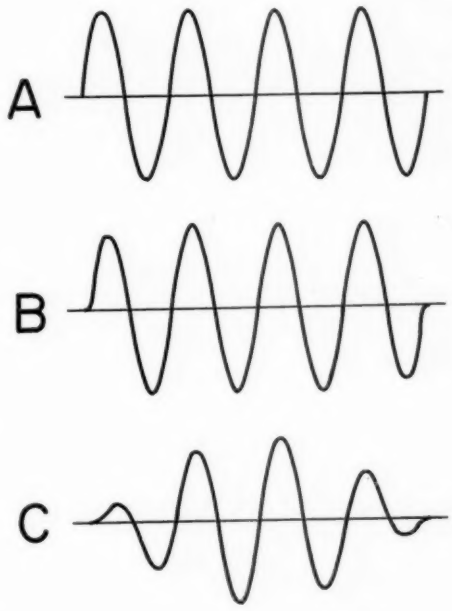

Fig. 2.—Three different types of 4-cycle oscillations for which frequency spectra (cf. Fig. 3) were determined. Burst *A* is an unmodified sinusoidal function, which, therefore, exhibits abrupt onset and offset. The abruptness of onset and offset is moderately reduced in burst *B* and greatly minimized in burst *C*. The mathematical expressions for these oscillations are given in the text.

A mechanical system consists of masses, elastances, and frictional resistance to displacement. The response of such a system to a unit impulse is known as its memory (or weighting) function.[14] The simplest example of a memory function is that derived from an underdamped simple harmonic oscillator (characterized by a single mass concentrated at a point, movement restricted to a rectilinear locus, elastic restoring force directly proportional to displacement from the position of rest, and frictional drag directly proportional to velocity of movement). When this oscillator is subjected to a unit impulsive force at zero time, the resulting motion is a sinusoid with exponential decay. The equation of motion (memory function) is

$$f(t) = \frac{1}{\sqrt{1 - k^2}\,\omega_0} e^{-k\omega_0 t} \sin \sqrt{1 - k^2}\,\omega_0 t \qquad (9)$$

where k is the coefficient of damping and ω_0 is $\sqrt{\text{elastance/mass}}$. Inserting this time-domain function into Equation 2 gives the associated frequency-domain function

$$g(\omega) = \frac{1}{(k\omega_0 + i\omega)^2 + (\sqrt{1 - k^2}\,\omega_0)^2} \tag{10}$$

This expression can be reduced to the useful form

$$\left| g(\omega) \right| = \frac{2}{\omega_0^2} \frac{1}{\sqrt{(1 - \alpha^2)^2 + 4k^2\alpha^2}} \tag{11}$$

where $\alpha = \omega/\omega_0$, and $\omega \geq 0$.

Fig. 4 illustrates the frequency spectrum of the above memory function (cf. Equation 11) for damping coefficients, k, of 0.5, 0.25, 0.125, and 0.0625, respectively. Each individual spectrum peaks at the abscissal value of $\alpha = \sqrt{1-2k^2}$, and the peak amplitudes are very nearly inversely proportional to k. It is of considerable interest that the frequency spectrum of the memory function has the same form as the response curve of the system to forced oscillations. It is also of interest that moderately damped memory functions are relatively rich in zero and near-zero frequency components. Undoubtedly this property explains, at least in part, why clinical spectrograms of heart sounds tend to be rich in low-frequency content.

The more general type of memory function consists of the sum of several decaying oscillations, each of which has its own particular value of ω_0 and k. It seems rather obvious that the frequency spectrum of such a function would tend to be both complicated and unrevealing.

PHYSICAL MEANING OF FREQUENCY SPECTRA

The frequency spectra of mechanical systems undergoing sustained periodic oscillations generally have a clear and physically real interpretation. In the case of transient oscillations, however, the interpretation of the frequency spectrum is decidedly more obscure, since a conceptual artifice is necessary to render exact mathematical formulation possible. Nevertheless, because certain physically real implications are inherent in the frequency spectrum of a transient sound, a closer look into the significance of the spectrum concept seems warranted.

In an earlier section, Equation 3 shows how the frequency-domain (frequency-spectrum) characteristics of transient oscillations are determined from their time-domain expression. The opposite operation may be performed according to the inversion process

$$f(t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} g(\omega)\, e^{i\omega t}\, d\omega \tag{12}$$

where the symbols have the same significance as previously given. In effect, this

equation represents an extension of Fourier's series to the limiting form, and thus includes sinusoidal components of all possible frequencies.[11]

Fig. 5 illustrates the physical interpretation of the inversion integral in the specific case of a 3-cycle train of sinusoidal oscillations, taken three quarters of a cycle after the onset of the oscillations. The convoluted spatial curve, *A*, is a graphic representation, at the stated time, of $g(\omega)\ e^{i\omega t}/2\pi$ for frequencies of positive sign. The multifoliate curve, *B*, is a projection of *A* on the complex plane, $\omega = 0$; as such, it represents, in effect, a polar coordinate plot of the frequency spectrum. The real component of the spatial curve is obtained by projection on a horizontal plane (curve *C*). The magnitude of oscillatory deflection at the stated instant of time, which is what f(t) signifies, is the algebraic area under curve *C*.

In order to avoid unnecessary complexity of Fig. 5, the negative frequency portion of the spatial curve, *A*, has been omitted. However, some of the negative frequency portion of the horizontal plane projection, curve *C*, is included in the illustration, and shows that the real components are identical for paired positive and negative values of frequency. Because of this circumstance it was not necessary to include negative frequencies in the spectrograms of Figs. 1, 3, and 4.

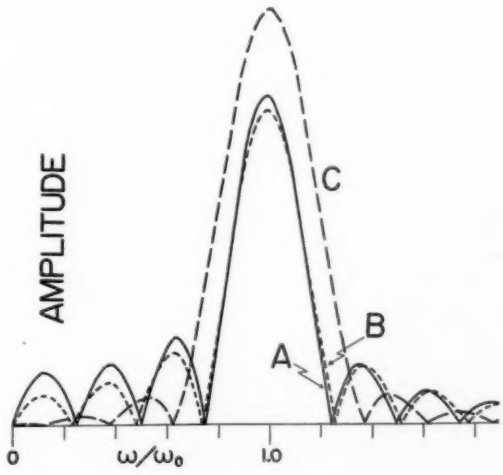

Fig. 3.—Frequency spectra, labeled respectively, of the three types of 4-cycle oscillations shown in Fig. 2. It is evident from this figure that reducing the abruptness of onset and offset of the oscillations produces relative reduction of the high- and low-frequency content of their spectrograms. Further discussion in text.

Also not shown in Fig. 5 is the imaginary component of the inversion integral, which consists of the area under a curve obtained by projecting the spatial curve, *A*, on a vertical plane which is parallel to the frequency axis. In the case of the n-cycle or $(n + \frac{1}{2})$-cycle sinusoidal burst (of which Fig. 5 is an example), the imaginary component of the inversion integral may be disregarded since it is zero.

Fig. 5, then, shows the time- and frequency-domain interrelationships of a simple, n-cycle sinusoidal burst of oscillations, "frozen" at a given instant of

time. Time progression is represented as a uniform, helical uncoiling of the convoluted curve. In the particular example illustrated, the convoluted curve would be completely uncoiled halfway through the 3-cycle burst of oscillations, and would lie entirely within a vertical plane. After this particular instant of time, the spatial curve would begin to coil up, with increasingly tighter convolutions, into a right-handed configuration.

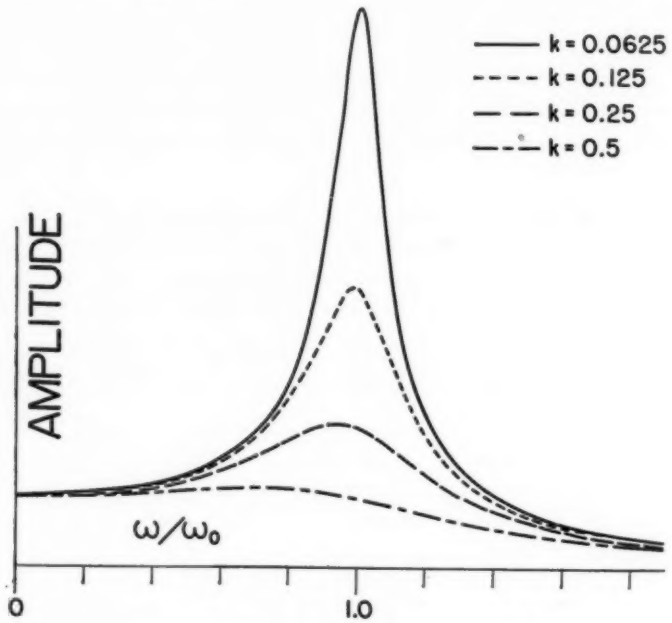

Fig. 4.—Frequency spectra of a simple memory function with various coefficients of damping, *k*. It is evident that for moderate degrees of damping (e. g., a coefficient of 0.25 or greater) the spectrogram is quite rich in zero and near-zero frequency components. This probably explains why clinical spectrograms of heart sounds not uncommonly extend down to the near-zero frequency range. Further discussion in text.

DISCUSSION

The representative frequency spectra with which this report is illustrated (Figs. 1, 3, and 4) show the distribution of frequency components which are associated with entire vibratory complexes. In this respect they differ from the usual type of clinical spectrophonocardiogram, since the latter is more concerned with displaying instant-by-instant changes in the frequency content of sonic vibrations. However, both types of analysis are intimately related to each other because they are both tied to the concept that sound-energy transients may be represented by a spectrum which contains continuous frequency components.

The relative merits of spectrophonocardiography have been rather well demonstrated in the case of sustained sounds such as cardiac murmurs. For instance, oscillograms of the typical systolic ejection murmur of aortic stenosis show a characteristic "diamond shaped" envelope,[15] whereas the spectrogram has a "Christmas tree" configuration.[16] These two types of pattern indicate, respectively, that both intensity and "pitch" wax during approximately the initial half of the murmur, and wane during the terminal portion. The two dif-

ferent types of registration are complementary in this example because changes in frequency are more clearly appreciated in the spectrogram, whereas changes in intensity are better recognized in the oscillogram. In the case of musical murmurs the spectrogram provides rather vivid visualization of harmonic content and variations in pitch during the course of the murmur. To cull the same information from the oscillogram of the murmur would be, at best, a laborious and time-consuming procedure.

In contrast to the case of cardiac murmurs, the frequency spectrograms of transient heart sounds are essentially artefacts in the same sense that the Fourier integral is a kind of mathematical artifice. This fact does not preclude the possibility that important information may be contained in the spectrogram of a heart-sound transient. Fig. 3, for example, indicates how the "snappiness" of such sounds might be quantitatively evaluated from their spectrograms. In addition to this a priori type of analysis there is the further possibility that important diagnostic information might come to be recognized on the basis of purely empirical clinical correlation.

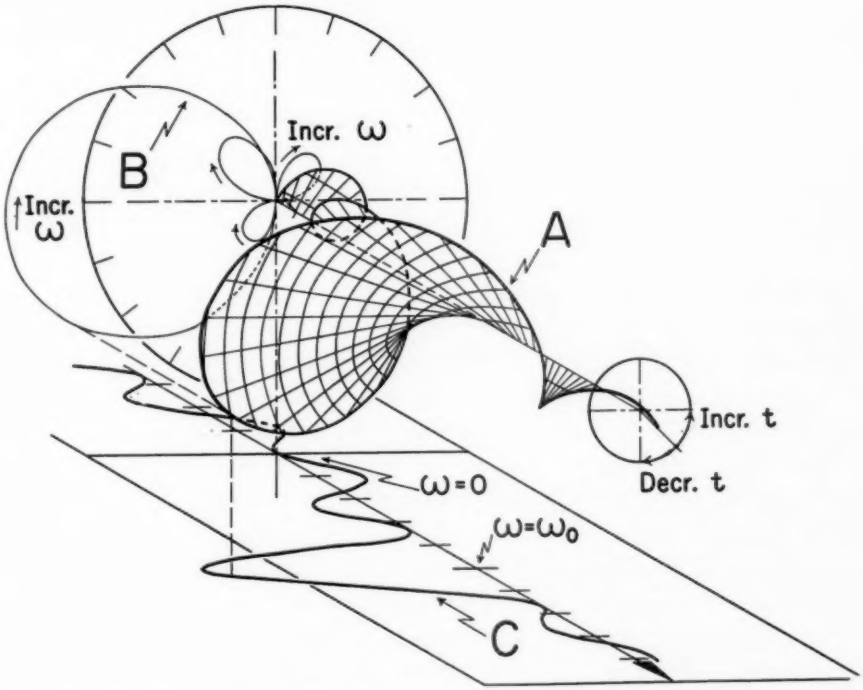

Fig. 5.—Graphic illustration of the inversion process by which the oscillographic properties of vibrations can be derived from their spectrogram (transformation from the frequency-domain to the time-domain). The convoluted spatial curve, *A*, is derived from the application of the Fourier integral to a 3-cycle burst of sinusoidal oscillations. In contrast to a Fourier series, the spatial curve, *A*, shows the amplitude and phase of a *continuous and infinite number of frequency components*, rather than of a finite number of discrete and regularly spaced frequency components. Time progression produces uniform uncoiling of the convoluted curve, and then increasingly tighter coiling in the opposite direction. Projection of the spatial curve on a plane normal to the frequency axis (curve *B*) is in essence a polar plot of the frequency spectrum. Curve *C*, which is obtained by projecting the spatial curve on a horizontal plane, is real in the mathematical sense. The oscillographic deflection at the given instant of time is equal to the algebraic area under curve *C*. (The illustration shows that the relationship between the oscillogram and spectrogram of a transient sound is not simple. It shows, furthermore, that the spectrogram of such a sound is an artefact in the broad sense of the term.)

In this report, we have limited ourselves to a consideration of various fixed-frequency oscillations. In a previous report,[17] we determined the simple harmonic components of some variable-frequency oscillations, and found that they consisted of a carrier frequency and numerous side frequencies. We find that combining the individual spectrograms of all of these harmonic components produces a spectrogram which somewhat resembles that of a "white noise" band, and which does not appear to reveal any specific information regarding the fundamental dynamics of the original oscillations.

We are not certain at this time what special significance may be ascribed to slurs and notching in conventional oscillographic phonocardiograms, but it is likely that such knowledge will be acquired as the science of stethography developes. In any event, it should be emphasized that for theoretical as well as technical reasons, such slurring and notching is virtually unrecognizable in the spectrogram, whereas it is strikingly evident in the oscillographic phonocardiogram. Somewhat parenthetically, it may be pointed out that so-called logarithmic phonocardiograms are essentially second derivatives of the sound energy, and, therefore, may provide considerable insight into the dynamics of the sonic generator.

SUMMARY

The theory of Fourier transform pairs is a profound mathematical concept which undoubtedly underlies the interrelationships between oscillographic and spectrographic types of phonocardiography. This communication introduces the concept of the Fourier transformation into the clinical phonocardiographic literature for what is apparently the first time.

Various simple harmonic oscillations, occurring in bursts of n or $(n + \frac{1}{2})$ cycles, are analyzed by means of the Fourier transform method, and are discovered to contain significantly large frequency components extending from the near-zero range to beyond twice the fundamental frequency of the oscillations. The spread of sizable frequency components is found to be directly related to the abruptness of the onset and offset of sonic energy.

The frequency spectra of simple memory functions have been determined in a like manner, and found to be of the same form as the frequency response of a damped, simple harmonic oscillator to forced oscillations. The relative magnitude of the near-zero frequency components is found to increase proportionately with the degree of damping of the system. This circumstance probably explains why sizable near-zero frequency components are commonly present in clinical spectrophonocardiograms.

An attempt is made, on predominantly theoretical grounds, to compare the relative merits of stethographic oscillograms and spectrograms. It is concluded that spectrograms may be rather valuable in the analysis of murmurs, especially the musical variety. However, in the case of sounds produced by closure of the valves, it appears that frequency spectrograms are essentially artefacts (in the broad sense of the term), and that they tend to obscure many important dynamic characteristics of transient heart sounds. On the basis of

these various considerations, we believe that frequency spectrography is a useful adjunctive procedure, but not necessarily the stethographic method of choice.

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The Vectorcardiographic QRSsÊ-Loop Findings in Chronic Cor Pulmonale

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There have been comparatively few detailed reports on the vectorcardiographic QRSsÊ-loop findings in cases of chronic emphysema with and without chronic cor pulmonale. The purpose of this paper is to describe the QRSsÊ-loop patterns observed in 42 cases of pulmonary emphysema with and without accompanying chronic cor pulmonale, and to correlate these findings with the QRS abnormalities in the electrocardiogram.

MATERIAL AND METHOD

In all of the 42 cases composing the study series there was symptomatic and/or radiographically demonstrable pulmonary emphysema of at least moderate severity. In 26 of the 42 cases there was either autopsy (8 cases) or radiographic evidence (18 cases) of right ventricular enlargement and/or chronic cor pulmonale.†

The standard 12-lead electrocardiogram was recorded in all patients, and, in addition, Leads V_{3R} and V_7 were taken in some cases. The vectorcardiograms were displayed on the Sanborn Viso-Scope and photographed on film with the DuMont oscilloscopic camera. Grishman's cube system of vectorcardiographic leads[1] was used to record the planar projections of the vectorcardiogram. The reference frame utilized in expressing the orientation of the mean manifest electrical axis of QRS (ÂQRS) and of the maximal mean instantaneous vectors of the planar projections of the QRSsÊ loop is marked off superiorly in minus 30 degree segments in a counterclockwise direction, and inferiorly in plus 30 degree segments in a clockwise direction from 0 degrees to 180 degrees. In the horizontal and frontal planes, 0 degrees is situated to the left, and in the right sagittal plane it is located anteriorly. Plus 90 degrees lies inferiorly in the frontal and right sagittal projections, and anteriorly in the horizontal projection.

RESULTS

I. *Vectorcardiographic Findings.*—The over-all results of this vectorcardiographic study are presented in Tables I through IV. The vectorcardiograms of the 42 patients composing the study series could be divided into four groups

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†X-ray diagnosis of chronic cor pulmonale was made on the basis of enlargement of the main pulmonary artery and/or right ventricular outflow tract.

according to the characteristics of the QRSsÊ loop. The QRSsÊ-loop findings in these four groups of vectorcardiograms are designated, respectively, Type A, Type B, Type C, and right ventricular enlargement (RVE) QRSsÊ-loop "patterns."

Type A QRSsÊ-loop pattern: The QRSsÊ loop in this type of pattern was distinguished by a relatively large terminal deflection of the loop to the right, posteriorly, and superiorly; the QRSsÊ loop otherwise differed little from the normal in many cases (Fig. 1). Of the 10 patients with this vectorcardiographic pattern, 2 had roentgenographic evidence of combined ventricular hypertrophy, and the other 8 had normal cardiovascular silhouettes. Vectorcardiograms which show the features just described as being characteristic of the Type A QRSsÊ-loop pattern are not uncommonly recorded from young adults, adolescents, and children, but are relatively infrequently observed in older adults without cardiopulmonary disease.

Type B QRSsÊ-loop pattern: In the vectorcardiograms in this group, the QRSsÊ loops were characterized by very large late mean instantaneous vectors which were oriented to the right and either superiorly or inferiorly, and which extended very far posteriorly. Thus, the posterior extent of the QRSsÊ loop in the Type B pattern was much greater than the leftward or rightward extent of the loop, whereas the initial deflection of the loop to the right and anteriorly was usually diminutive (Fig. 2). The QRSsÊ loop in the horizontal projection was inscribed counterclockwise in its entirety, whereas the right sagittal QRS loop was usually inscribed clockwise. Of the 16 patients whose vectorcardiograms displayed a Type B pattern, 11 had roentgenographic evidence of chronic cor pulmonale, including 2 with autopsy-proved right ventricular hypertrophy. One of the other 5 patients without roentgenographic abnormality of the heart came to autopsy and was also found to have right ventricular enlargement.

Type C QRSsÊ-loop pattern: The QRSsÊ loop of the Type C pattern typically displayed a large rightward and posteriorly directed terminal deflection, which in all but 2 of the cases was also oriented superiorly. The magnitude of the maximal mean instantaneous vector of this terminal rightward deflection was such that the rightward projection of the loop in the Type C pattern greatly exceeded both the leftward and posterior dimensions of the loop. As a general rule, the horizontal QRS loop had a figure-of-eight configuration with a counterclockwise-inscribed early leftward component and a clockwise-inscribed terminal rightward component (Fig. 3). Both right sagittal and frontal QRS loops were almost invariably inscribed clockwise. Three of the 7 patients in this group had roentgenographic evidence of right ventricular enlargement or cor pulmonale, and 2 of the others who had normal cardiac silhouettes came to autopsy and were found to have right ventricular enlargement.

Thus, about 75 per cent of combined groups B and C consisted of cases with radiologic or autopsy evidence of right ventricular enlargement or cor pulmonale. This percentage would undoubtedly have been even higher if more autopsy cases had been available. The authors feel reasonably justified in concluding that the Types B and C loop patterns, when recorded from patients with chronic pulmonary emphysema, are the equivalent of the more familiar loop patterns of right ventricular enlargement which are described in the following paragraph.

TABLE I. TYPE A QRSsÊ-LOOP PATTERN

CASE NUMBER	CLINICAL DIAGNOSIS OF CHRONIC COR PULMONALE	X-RAY	AUTOPSY	HORIZONTAL QRS LOOP		RIGHT SAGITTAL QRS LOOP		FRONTAL QRS LOOP		ÂQRS	QRS_{V_1}			QRS_{V_6}	
				MAX. VECTOR	DIRECTION OF INSCRIPTION	MAX. VECTOR	DIRECTION OF INSCRIPTION	MAX. VECTOR	DIRECTION OF INSCRIPTION		CONFIGURATION	R (MM.)	Q OR S (MM.)	R (MM.)	S (MM.)
21.	0	N	—	−10°	CC	−160°	CC	+10°	CC	+60°	rS	0.2	3	5.5	1
22.	0	N	—	+10°	CC	−160°	CC	−10°	CC	−70°	rS	1.5	5	4	3
23.	0	LVE and RVE	—	−20°	CC	−175°	C	+25°	C	+90°	rS	1.2	3	13	8
24.	0	N	—	−25°	CC	180°	C	+20°	C	+70°	rS	0.6	16	4	4
25.	+	N	—	−10°	CC	180°	C	+10°	C	+60°	rS	2	7	3	1
26.	0	N	—	−20°	CC	+120°	C	+20°	CC	+60°	rS	3	10	17	0
27.	+	N	—	+10°	CC	+85°	C	+45°	C	+80°	rS	1,5	3	4	3
28.	+	N	—	−10°	CC/C	−165°	C	−10°	C/CC	+100°	rS	1.5	2	9	11
33.	0	N	—	−10°	CC	−155°	C	+15°	C/CC	+60°	rS	0.2	5	3	0.5
37.	+	LVE and RVE	—	−25°	CC	−165°	C	+15°	CC	−100°	rS	0.2	7	1	3.5
		Range		−25° to +10°		+85° to −155°		−10° to +45°		−100° to +100°		0.2 to 3	2 to 16	1 to 17	0 to 11
		Average		−10°		+172°		+17°		+77°		1.2	6.1	6.4	3.5

N: Normal. CC: Counterclockwise inscription. C: Clockwise inscription. CC/C: Counterclockwise inscription of the proximal portion of the loop and clockwise inscription of the distal portion. C/CC: Clockwise inscription of the proximal portion of the loop and counterclockwise inscription of the distal portion. LVE and RVE: Left and right ventricular enlargement.

TABLE II. TYPE B QRSsÊ-LOOP PATTERN

CASE NUMBER	CLINICAL DIAGNOSIS OF CHRONIC COR PULMONALE	X-RAY	AUTOPSY	HORIZONTAL QRS LOOP		RIGHT SAGITTAL QRS LOOP		FRONTAL QRS LOOP		ÂQRS	QRSV1			QRSV6	
				MAX. VECTOR	DIRECTION OF INSCRIPTION	MAX. VECTOR	DIRECTION OF INSCRIPTION	MAX. VECTOR	DIRECTION OF INSCRIPTION		CONFIGURATION	R (MM.)	Q OR S (MM.)	R (MM.)	S (MM.)
9.	+	N	RVH	−105°	CC	180°	C	+150°	C	+120°	rS	5	10	3	5
10.	+	CCP	—	−60°	CC	−170°	CC	−30°	C	−10°	rS	0.6	5.5	5	0.4
11.	+	CCP	—	−120°	CC	−140°	CC	−130°	CC	−90°	rS	0.3	8	3	8
12.	+	CCP	—	−120°	CC	+170°	C	+130°	C	+80°	rS	0.3	5	1.6	2.5
13.	+	CCP	—	−110°	CC	+140°	CC	+85°	C	+90°	rS	0.5	3	0.3	4
14.	+	CCP	—	−90°	CC	+160°	CC	+70°	C	+80°	rS	0.6	8	3	0
15.	+	CCP	—	−95°	CC	−170°	C	+35°	C	+80°	rS	1.5	11	1	3
16.	+	CCP	—	−115°	CC	−160°	C	+55°	C	+90°	rS	0.2	8	1.5	1.5
29.	0	N	—	−115°	C	+175°	C	+70°	C	+80°	rS	3	6	1.8	5
31.	+	N	—	−85°	CC	−160°	C	+10°	CC	+60°	QS	0	5	1.5	0
32.	0	N	—	−65°	CC	+160°	C	+35°	C	+70°	rS	1	20	8	1
34.	+	N	—	−90°	CC	+170°	CC/C	+40°	C	+90°	rS	0.4	7	2.5	1
35.	+	CCP	—	−85°	CC	−150°	C	+25°	C/CC	+90°	rS	0.6	7	4	10
38.	+	CCP	—	−100°	CC	+145°	C	+70°	C	+80°	rS	0.4	6	0.2	6
40.	+	CCP	RVH	−40°	CC	+135°	C	+55°	C	+10°	rS	0.6	3.5	7.5	0.5
41.	+	CCP	RVH	−100°	CC	−170°	C	+30°	CC	+60°	rS	1.8	12	8	0.5
		Range		−40° to −120°		+135° to −140°		−30° to −130°		−90° to +120°		0 to 5	3 to 20	0.2 to 8	0 to 10
		Average		−107°		+177°		+60°		+61°		1	7.8	3.2	3

N: Normal. CC: Counterclockwise inscription. C: Clockwise inscription. CC/C: Counterclockwise inscription of the proximal portion of the loop and clockwise inscription of the distal portion. C/CC: Clockwise inscription of the proximal portion of the loop and counterclockwise inscription of the distal portion. CCP: Chronic cor pulmonale.

TABLE III. TYPE C QRSsÊ-LOOP PATTERN

CASE NUMBER	CLINICAL DIAGNOSIS OF CHRONIC COR PULMONALE	X-RAY	AUTOPSY	HORIZONTAL QRS LOOP		RIGHT SAGITTAL QRS LOOP		FRONTAL QRS LOOP		ÂQRS	QRS_{V_1}			QRS_{V_6}	
				MAX. VECTOR	DIRECTION OF INSCRIPTION	MAX. VECTOR	DIRECTION OF INSCRIPTION	MAX. VECTOR	DIRECTION OF INSCRIPTION		CONFIGURATION	R (MM.)	Q OR S (MM.)	R (MM.)	S (MM.)
1.	+	RVE	—	−160°	CC/C	+170°	CC	+170°	C	+120°	qrs	0.5	2	2	2
2.	+	N	RVH	−120°	CC/C	180°	C	+170°	C	+120°	rsR′	4	1	5	8
5.	+	N	RVH	−130°	CC	+105°	C	+140°	C	+120°	rs	0.5	7	3	2
7.	+	CCP	—	−150°	CC/C	−130°	CC	−150°	C	−120°	rs	2	3	0.3	3.5
18.	+	CCP	—	−140°	CC/C	+90°	C	+60°	C	+120°	rsR′s′	7	2.5	3.5	3
20.	+	N	—	180°	CC	−90°	C	−125°	CC	−90°	qr	1.5	1	4	3
36.	+	N	—	−130°	CC/C	−155°	C	+40°	C	+100°	rS	2.5	10	3.5	10
		Range		180° to −120°		+90° to −90°		+40° to −125°		+100° to −90°		0.5 to 7	1 to 10	0.3 to 5	2 to 10
		Average		−144°		+179°		+146°		+105°		2.6	3.8	3	4.5

N: Normal. C: Clockwise inscription. CC: Counterclockwise inscription. CC/C: Counterclockwise inscription of the proximal portion of the loop and clockwise inscription of the distal portion. CCP: Chronic cor pulmonale.

TABLE IV. RVE QRSŝÊ LOOP

CASE NUMBER	CLINICAL DIAGNOSIS OF CHRONIC COR PULMONALE	X-RAY	AUTOPSY	HORIZONTAL QRS LOOP		RIGHT SAGITTAL QRS LOOP		FRONTAL QRS LOOP		ÂQRS	QRS_{V1}			QRS_{V6}	
				MAX. VECTOR	DIRECTION OF INSCRIPTION	MAX. VECTOR	DIRECTION OF INSCRIPTION	MAX. VECTOR	DIRECTION OF INSCRIPTION		CONFIGURATION	R (MM.)	Q OR S (MM.)	R (MM.)	S (MM.)
3.	+	N	—	−120°	C	+150°	CC	+30°	C	+120°	rS	0.5	4	5	3
4.	+	No x-ray	RVH	+150°	C	+30°	CC	+170°	C	+120°	qR	4	1	6.5	5.5
6.	+	CCP	RVH	+150°	C	+60°	CC	+140°	C	+120°	rS	0.2	5	2.5	2
8.	+	CCP	RVH	+135°	C	+15°	CC	+150°	C	+120°	rsR′	8	3	3	7
17.	+	CCP	—	−110°	C	−170°	C	−130°	C	+120°	rsR′s′	4	3	2.5	8
19.	+	RVE	—	+150°	C	+120°	CC	+130°	CC	+70°	rSR′	2	1.5	3	2
30.	+	N	—	0	C	+90°	CC	+15°	C	+50°	rSR′	5	3	6	1.5
39.	+	CCP	—	+140°	C	+5°	CC	+170°	C	+100°	QR	3.2	2.5	5	5
42.	+	RVE	—	+140°	C	+10°	CC/C	+170°	C/CC	+150°	rSr′	2.2	2	2	5
		Range		0° to −110°		+5° to −170°		+15° to −130°		+50° to +150°		0.5 to 8	1 to 5	2 to 6.5	1.5 to 8
		Average		+144°		+74°		+130°		+108°		3.2	2.8	3.9	4.3

N: Normal. C: Clockwise inscription. CC: Counterclockwise inscription. CC/C: Counterclockwise inscription of the proximal portion of the loop and clockwise inscription of the distal portion. C/CC: Clockwise inscription of the proximal portion of the loop and counterclockwise inscription of the distal portion. CCP: Chronic cor pulmonale. RVE: Right ventricular enlargement.

TABLE V. CORRELATION OF VECTORCARDIOGRAPHIC AND ELECTROCARDIOGRAPHIC FINDINGS IN COR PULMONALE

	QRSsÊ-LOOP PATTERN							
	A		B		C		RIGHT VENTRICULAR ENLARGEMENT	
	WITH CCP	WITHOUT CCP	WITH CCP	WITHOUT CCP	WITH CCP	WITHOUT CCP	WITH CCP	WITHOUT CCP
Number of cases	2	8	12	4	5	2	7	2
ÂQRS: +110° to −90°	1	1	1	0	5	1	6	1
R/S_{V1} or $R/Q_{V1} > 1$	0	0	0	0	2	1	6	1
$R/S_{V6} < 1$	1	1	7	1	3	1	3	0
Number of cases satisfying one or more criteria	1	1	7	1	5	2	7	2

CCP: Chronic cor pulmonale.

Right ventricular hypertrophy QRSsÊ-loop pattern: The cases in this group showed definite vectorcardiographic evidence of right ventricular enlargement, i.e., displacement of the greater portion of the QRSsÊ loop anteriorly and to the right, with clockwise inscription of the horizontal QRS loop and absence of slowed inscription of any portion of the loop (Fig. 4). There were 9 patients in this group, 6 with evidence on the chest film of cor pulmonale or right ventricular enlargement (2 of these with autopsy confirmation of this diagnosis), and 3 without roentgenographic evidence of cardiac abnormality (although anatomic right ventricular hypertrophy was seen in one of these patients at autopsy).

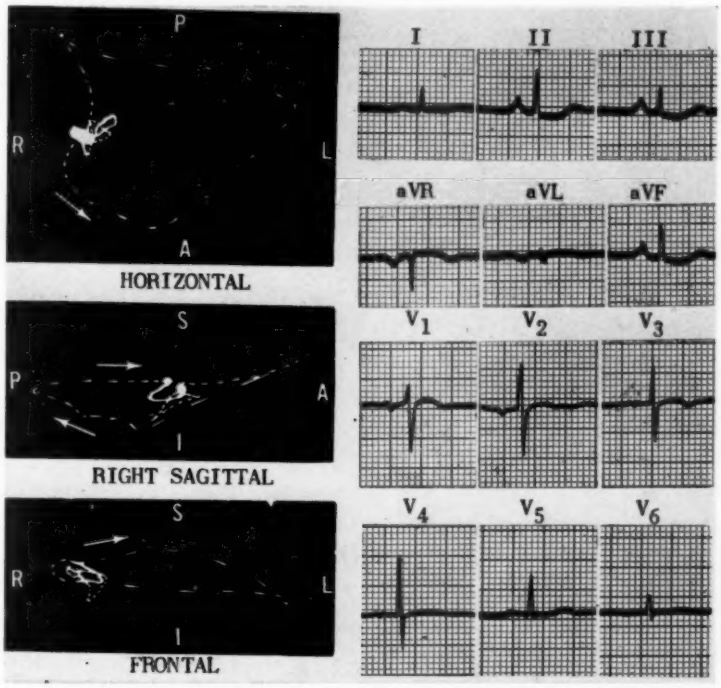

Fig. 1.—Type A QRSsÊ-loop pattern recorded from a patient with chronic pulmonary emphysema. Note the rightward and posteriorly directed terminal deflection of the horizontal QRS loop.

II. *Electrocardiographic Findings.*—Although many criteria for the diagnosis of right ventricular enlargement have been proposed by different investigators,[2-5] the authors have chosen to evaluate only the following: (1) right axis deviation of ÂQRS to the right of +110°; (2) R/S or R/Q in Lead $V_1 > 1$; and (3) R/S in Lead $V_6 < 1$ (Table V).

In only 12 of the patients of this series was ÂQRS to the right of +110° (Table V). There were 13 patients with roentgenographic or autopsy evidence of chronic cor pulmonale and/or right ventricular enlargement whose electrocardiograms did not show right axis deviation, and there was an equal number of patients without autopsy or radiologic evidence of right ventricular enlargement and/or cor pulmonale whose electrocardiograms likewise did not show this finding. In other words, 26 of the total 42 patients in the series presented radiographic

or postmortem evidence of chronic cor pulmonale and/or right ventricular enlargement, and 50 per cent of these evidenced right axis deviation of ÂQRS in the electrocardiogram. Of the other 16 patients without evidence of chronic cor pulmonale and/or right ventricular enlargement by examination or at autopsy, only 3 displayed right axis deviation of ÂQRS in the electrocardiogram. Seven of the 16 patients with right axis deviation of ÂQRS belonged to the group with vectorcardiographic evidence of right ventricular hypertrophy. Six patients with right axis deviation of ÂQRS presented the Type C QRSsÊ-loop pattern, and 2 patients, the Type A configuration, whereas the Type B QRSsÊ-loop pattern was associated with right axis deviation of ÂQRS in only one instance.

For the most part, the electrocardiographic findings in a given case correlated closely with the QRSsÊ-loop findings in the vectorcardiogram. It is readily apparent that as a general rule, Lead V_6 will display a terminal S wave no matter which QRSsÊ-loop pattern of the four types described in this report happens to be recorded in the vectorcardiogram, since each of these loop patterns exhibits terminal rightward instantaneous vectors. However, certain differences exist between these four groups of cases with respect to the appearance of the precordial electrocardiogram. As will be remembered, the horizontal QRS loop in the Type A QRSsÊ-loop pattern is normal in both appearance and orientation, with the exception of a rightward and posterior terminal deflection. Since it is the latter component of the QRSsÊ loop which produces the terminal S wave in Lead V_6, rather than posterior rotation of the loop itself, it is not surprising that the S wave in Lead V_6 of the electrocardiograms in this group rarely equaled or exceeded in size the R wave in the same lead (only 2 of the 10 cases having an R/S amplitude ratio in Lead V_6 of less than 1, and only 1 additional case having an R/S ratio equal to 1). In other words, "clockwise rotation" as indicated in the precordial leads by a leftward shift of the QRS transition point is not a characteristic feature of the electrocardiograms of the group with Type A QRSsÊ loops.

In contrast to the Type A QRSsÊ-loop pattern, the horizontal QRS loop in the Type B QRSsÊ-loop pattern not only displays large terminal rightward and posterior mean instantaneous vectors but the long axis of the loop is rotated far posteriorly. As a result, the R waves in the left precordial leads of the electrocardiogram are diminished in amplitude, but the S waves in these leads gain in depth. In 8 of the 16 cases in the Type B group the R/S amplitude ratio in Lead V_6 was less than 1 (and in 1 case it equaled 1). Therefore, the precordial transition point for QRS is shifted to the left, and ÂQRS is rotated posteriorly ("clockwise rotation," in conventional terminology). Since the initial rightward and anterior deflection of the horizontal QRS loop in the Type B QRSsÊ-loop pattern is typically diminished, it is not surprising that the initial R waves in the right precordial leads tend to be quite small, and the S waves are of great depth. This can sometimes lead to the erroneous electrocardiographic diagnosis of old anteroseptal infarction.

As will be recalled in the Type C QRSsÊ-loop pattern, the horizontal QRS loop is written in a counterclockwise direction at first, almost directly to the left, but it soon turns and is written rapidly from left to right. The loop then continues to be inscribed in a clockwise direction far to the right and somewhat posteriorly,

to produce a large rightwardly directed terminal deflection which is the dominant feature of the horizontal projection of the vectorcardiogram. Thus, in the Type C QRSsÊ-loop pattern the rightward extent of the horizontal QRS loop greatly exceeds the earlier leftward extent of the loop. This is reflected in Lead V_6 of the electrocardiogram by an R/S amplitude ratio of less than 1, a finding present in 4 of the 7 cases in this group. Of the 9 cases in which the vectorcardiograms showed QRSsÊ-loop patterns of right ventricular enlargement, only 3 cases presented in Lead V_6 the electrocardiographic finding of an R/S amplitude ratio of less than 1.

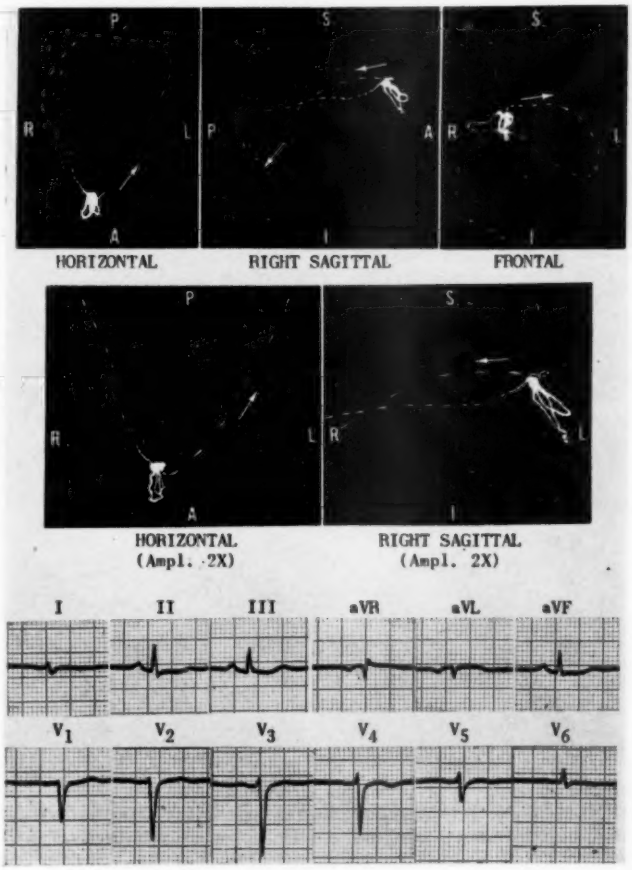

Fig. 2.—Type B QRSsÊ-loop pattern recorded from a patient with radiographic evidence of chronic cor pulmonale due to chronic pulmonary emphysema. The marked posterior rotation of the QRSsÊ loop is quite evident in the horizontal projection of the vectorcardiogram. On the other hand, the TsÊ loop is directed anteriorly and, therefore, diverges abnormally from the QRSsÊ loop.

None of the patients whose vectorcardiograms displayed the Type A or B QRSsÊ-loop patterns had electrocardiograms which satisfied the authors' Lead-V_1 criterion for the diagnosis of right ventricular enlargement, namely, an R/S or R/Q ratio greater than 1. This result is not surprising when one remembers that the major axis of the QRSsÊ loop in the Type A pattern is oriented in an essentially normal direction, that is, to the left and posteriorly, whereas

in the Type B pattern the long axis of the QRSsÊ loop is directed more posteriorly than is usual. As a consequence, in each of these two groups, Lead V_1 typically records an rS deflection. On the other hand, the R/S or R/Q amplitude ratio in Lead V_1 exceeded 1 in 3 of the 7 cases in the Type C group, and in 7 of the 9 cases in the group with vectorcardiographic evidence of right ventricular enlargement. As previously indicated, the horizontal QRS loop in the Type C QRSsÊ-loop pattern has a figure-of-eight configuration, with both leftward and

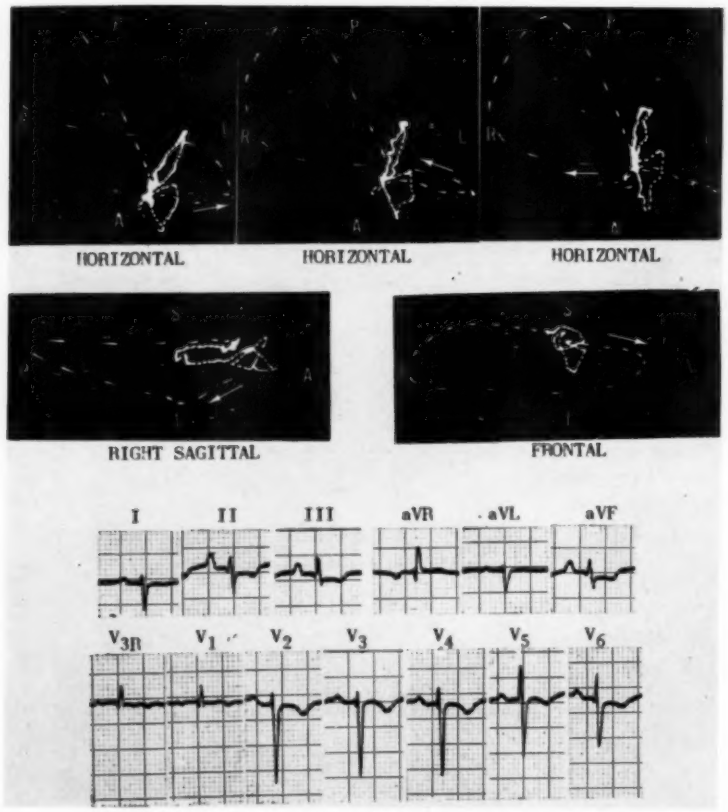

Fig. 3.—Type C QRSsÊ-loop pattern in the vectorcardiogram of a patient with x-ray evidence of clinically severe chronic cor pulmonale and right ventricular enlargement. The three horizontal projections of the vectorcardiogram reproduced in this figure demonstrate respiratory changes in the QRSsÊ-loop configuration, consisting, in the main, of a progressive anterior shift of the rapidly inscribed left-to-right limb of the horizontal loop. Note the large, clockwise-inscribed and rightwardly and posteriorly oriented terminal deflection of the horizontal QRS loop. The PsÊ-loop orientation and appearance are consistent with right atrial enlargement.

rightward components of the loop having an orientation more or less perpendicular to the lead axis of Lead V_1. As a result, minor variations in the anterior-posterior extent of either or both of these components of the horizontal QRS loop can cause Lead V_1 to record an rS, RS, or low amplitude, vibratory qrsr′, qrs, rsr′, or qr deflection. In 3 of the 7 cases in the Type C group, Lead V_1 registered rS deflections in which the S waves never attained the depth of S_{V1} observed in the Type B group, but often were slurred or notched at their nadir or on their

ascending limbs. In the other 4 cases in the Type C group, Lead V_1 of the electrocardiogram displayed vibratory qrs, rsr′(s′), or qr deflections, having an R/S or R/Q amplitude ratio greater than 1. The 7 patients in the group with vectorcardiographic evidence of right ventricular enlargement whose electrocardiograms satisfied the Lead-V_1 criterion for the diagnosis of right ventricular enlargement had either rsR′(s′) or QR deflections in Lead V_1. It is of some interest that in only 2 of the 10 cases in the group with R/S_{V1} or $R/Q_{V1} > 1$ was the amplitude of the R wave itself in this lead greater than 1.

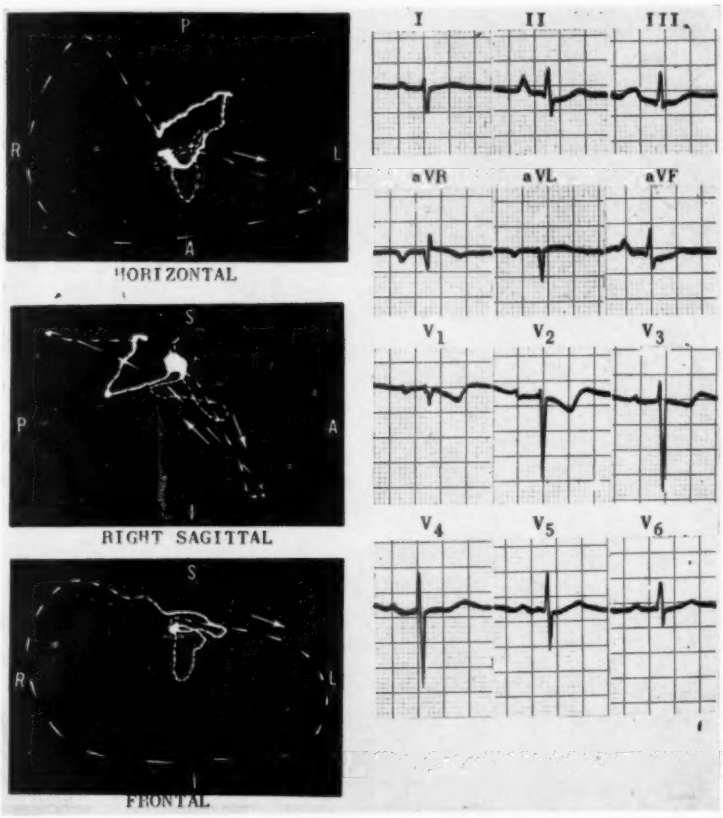

Fig. 4.—QRSsÊ-loop pattern of right ventricular enlargement recorded from the same patient as the loops in Fig. 3, although at a later date. Note that the horizontal QRS loop is now inscribed entirely clockwise, and for the most part is anteriorly oriented. The patient from whom this vectorcardiogram was recorded expired several months later, and postmortem examination confirmed the diagnosis of right ventricular hypertrophy and chronic cor pulmonale.

DISCUSSION

The evolution of cardiac abnormalities in chronic cor pulmonale has been observed both radiologically and pathologically[7] to pass through three stages: first, muscular hypertrophy of the right ventricle (particularly of the outflow tract) unaccompanied by chamber enlargement; second, right ventricular dilatation and thickening of the walls of the right ventricle; third, development of tricuspid insufficiency with right atrial enlargement and hypertrophy and enlargement of both inflow and outflow tracts of the right ventricle.

TABLE VI. EVOLUTION OF THE ANATOMIC AND RELATED VECTORCARDIOGRAPHIC AND ELECTROCARDIOGRAPHIC CHANGES IN CHRONIC COR PULMONALE

ANATOMIC ABNORMALITY	QRSsÊ-LOOP PATTERN	QRS CHANGES IN ELECTROCARDIOGRAM
(1) Hypertrophy of right ventricular outflow tract	Type A	(a) ÂQRS normally oriented (b) Terminal S waves in Leads I and V_6 with an R/S amplitude ratio greater than 1 in both of these leads
	Type B	(a) Posterior and rightward or medial rotation of ÂQRS (b) rS deflection in Lead V_6 with an R/S amplitude ratio of less than 1 (c) S wave of greater depth in Lead V_1 than in Type A
(2) Right ventricular dilatation and mural thickening	Type C	(a) Right axis deviation of ÂQRS—to the right of +110° (b) Low, vibratory qrs, rsR′, or qr deflections with an R/S or R/Q amplitude ratio greater than 1 in Lead V_1 (c) An rS deflection in Lead V_6 with an R/S amplitude ratio of less than 1
(3) Hypertrophy and dilatation of inflow and outflow tracts of the right ventricle	RVE	(a) Right axis deviation of ÂQRS—to the right of +110° (b) qR or rsR′ deflection in Lead V_1 with an R/S or R/Q amplitude ratio greater than 1 (c) An R/S deflection in Lead V_6 with an R/S amplitude ratio often less than 1

The right ventricular outflow tract consists of muscle of the conus arteriosus or infundibulum and includes basal right septal muscle and the crista supraventricularis. The basal right septum and the crista supraventricularis have been shown to be the last regions of the interventricular septum to undergo activation, and this occurs in an apex-to-base direction.[8-10] Thus, according to Sodi-Pallares and associates[10] and to Burchell,[8] activation of these regions gives rise to electrical forces directed to the right, posteriorly, and superiorly. Similarly, activation of the free wall of the conus arteriosus produces late forces directed to the right, superiorly, and slightly anteriorly. In most normal adults these late forces which emanate from the right ventricular outflow tract are dominated by electrical forces which arise in the basal left ventricular wall and are directed almost oppositely. However, with hypertrophy of the right ventricular outflow tract it would be reasonable to expect the appearance of late QRS forces directed to the right, posteriorly, and superiorly. It is possible therefore that the Type A QRSsÊ-loop pattern observed in the vectorcardiogram in some cases of chronic pulmonary emphysema, which is characterized by a prominent rightward, posterior, and superior terminal deflection of the QRSsÊ loop, may correspond to the initial stage in the evolution of the cardiac abnormalities occurring in chronic cor pulmonale and, therefore, may reflect early hypertrophy of the right ventricular outflow tract (Table VI). Further muscular hypertrophy of the right ventricular outflow tract may lead to a marked increase in the magnitude of the late QRS forces directed to the right, posteriorly, and superiorly. Moreover, the greater magnitude of these forces arising in the right ventricular outflow tract might enable them to become electrically preponderant earlier and, therefore, manifest themselves earlier in the QRS interval. The QRSsÊ loop of the vectorcardiogram reflects these changes in the balance of cardiac forces, perhaps by displaying a large late deflection rightwardly, posteriorly, and superiorly, and by showing displacement of its long axis posteriorly, superiorly and medially. The result would be the appearance of the Type B QRSsÊ-loop pattern. This explanation of the mechanism of the Type B pattern in chronic pulmonary emphysema and cor pulmonale is purely conjectural and does not take into account either the effects of anatomic rotation of the heart (which most certainly must occur during the development of chronic cor pulmonale) or the contributory factor of conduction delay.

Dilatation of the right ventricular chamber and hypertrophy of its free wall occur in the second stage of the evolution of the cardiac abnormalities in chronic cor pulmonale. The resulting anteriorly and inferiorly directed QRS forces of increased magnitude generated in the hypertrophied wall of the right ventricle would tend to manifest themselves earlier in the QRS interval than the augmented QRS forces arising in the right ventricular outflow tract, since the right ventricular free wall is normally activated before contraction of the outflow tract of the right ventricle. Accordingly, one would anticipate that the QRSsÊ loop of the vectorcardiogram would show anterior and inferior displacement of its mid-portion, the terminal portion of the loop retaining its rightward posterior and superior orientation. Again, the validity of this explanation of the genesis of the Type C QRSsÊ-loop pattern must remain open to question.

Finally, in the third and final stage of the evolution of the cardiac abnormalties in chronic cor pulmonale, the combination of dilatation of the right ventricular chamber and hypertrophy of both inflow and outflow tracts of the right ventricle gives rise in the vectorcardiogram to the typical QRSsÊ-loop pattern of right ventricular enlargement in which (a) the horizontal QRS loop is inscribed clockwise anteriorly, at first to the left and then to the right, and (b) the right sagittal QRS loop is inscribed counterclockwise anteriorly and inferiorly.

The QRSsÊ-loop patterns listed in Table VI along with the electrocardiographic findings are not specific diagnostically for chronic cor pulmonale but are observed in some cases of mitral stenosis as well.[11] Moreover, any of the above-mentioned QRSsÊ-loop patterns may be observed occasionally in the vectorcardiograms of adult subjects without detectable cardiopulmonary disease. Nevertheless, the presence of the Types B, C, or RVE, QRSsÊ-loop patterns in the vectorcardiograms of patients with chronic pulmonary emphysema generally constitutes fairly reliable, and sometimes the sole objective, evidence of coexisting chronic cor pulmonale.

SUMMARY

Four QRSsÊ-loop patterns observed in the vectorcardiograms of patients with chronic cor pulmonale due to emphysema are described in this paper and related to the associated electrocardiographic QRS findings. These clinical observations in the vectorcardiogram and electrocardiogram have been found to have a good correlation with the pathologically demonstrated evolution of anatomic cardiac abnormalities in chronic cor pulmonale.

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Precordial Isotope-Dilution Curves in Congenital Heart Disease: A Simple Method for the Detection of Intracardiac Shunts

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An easy method for the objective demonstration of intracardiac shunts would be of aid in screening patients suspected of having such shunts. Despite improved clinical diagnosis,[1] a definite diagnosis frequently requires the performance of cardiac catheterization. If a convenient, reasonably sensitive test for the presence of intracardiac shunts were available, the incidence of negative catheterizations should be lessened and additional data to indicate the necessity of catheterizations to detect the level of the shunts would be available.

The use of indicator-dilution curves has been of great value in the study of patients with shunts.[2,3] In general, these curves are obtained during cardiac catheterization and require that blood be sampled from an artery or the heart itself, whether the injected indicator is a dye,[4] saline solution,[5] or radioactive substance.[6,7]

Isotope-dilution curves recorded by focusing a scintillation probe over the precordium yield contours similar to arterial dye-dilution curves in patients without shunts when suitable collimation is used.[8,9] Determinations of cardiac output by this method compare favorably with conventional methods.[10-14] This technique, which requires only a venipuncture and appropriate detection equipment, theoretically should differentiate between patients with normal intracardiac circulations and those with abnormal intracardiac circulatory pathways. Preliminary reports from various laboratories, including this one, have noted characteristic changes in externally monitored isotope-dilution curves obtained from patients with shunts.[15-18] Utilizing peripheral and central injections, and simultaneously recording from probes focused over the heart and femoral artery, Greenspan and associates[19] have successfully detected and localized right-to-left shunts. These authors also reported alterations in the contour of the curves in the presence of left-to-right shunts.

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The purpose of this report is to present the experience of this laboratory in the application of precordial isotope-dilution techniques to this problem, and to attempt to systematize the differences found between a group of normal patients and a group of patients who were proved to have intracardiac shunts by conventional means.

MATERIALS AND METHODS

Thirty-four precordial isotope-dilution curves were analyzed from 22 control patients in whom repeated screening examinations were negative for heart disease. Thirty-four studies were analyzed from 19 patients who were proved to possess a central shunt by means of right heart catheterization. The patients were in the dorsal recumbent position during the procedure. The majority of the isotope curves were obtained at the time of catheterization, whereas the remainder were recorded during outpatient visits.

Pressures during right heart catheterization were recorded on a multichannel direct-writing recorder, utilizing either an electromanometer or a Statham P23Db pressure transducer. Values of blood oxygen were determined by the method of Van Slyke and Neill.[20] Duplicate determinations in this laboratory agree to within 0.2 volumes per cent. For the diagnosis of atrial septal defect a rise in oxygen of 1.5 volumes per cent over the mean caval values was required; rises of at least 1 volume per cent in the right ventricle and pulmonary artery over the downstream chambers were required for the diagnosis of shunts at those levels. When available, nitrous-oxide tests[21] were performed, and the results were in agreement with the oxygen data. Whenever possible, systemic and pulmonary blood flows were determined according to the Fick principle. Either the Scholander micro gas analyzer or the Beckman Model E2 oxygen analyzer was utilized for determinations of the percentage of oxygen in expired air.

A collimated scintillation detector was positioned in direct contact with the skin over the second left intercostal space, fourth left intercostal space, or the apex. The detector employed in the probe was a 1-inch by 1-inch thallium-activated sodium iodide crystal shielded with a 1-inch thick straight-bore collimator which had a diameter of 1 inch and a depth of 1½ inches beyond the crystal.

The scintillation probe was connected to a Nuclear-Chicago rate meter with a variable time constant set at 2.0 seconds. Dose was dependent on the selection of count rate, which ranged between 3,000 and 30,000 counts per minute. Curves were recorded on a direct-writing linear recorder with a paper speed of 6 inches per minute, in all but 1 patient in whom a semilog recorder was utilized.

The radioactive iodinated human serum albumin (RIHSA) was delivered into an antecubital vein via a three-way stopcock attached to an indwelling No. 20 Riley needle. The RIHSA, contained in a volume of 1 milliliter, was injected rapidly and followed immediately by a 10-milliliter saline flush. The time of injection was marked on the base line, and after the injection the curve was recorded through the primary phase and recirculation. Ten minutes after injection, a final dilution was recorded for 1 minute. Radioactivity of doses ranged from 2 to 30 microcuries per study, and adequate results were often obtained with the use of as little as 2 microcuries.

The blood volume was determined in about half of the series by the RIHSA method.[22] A single-channel gamma-ray spectrometer and scintillation-well counter were employed for the counting of blood samples and standard. In the remainder, blood volumes were estimated from normal standards.[23]

The curves were extrapolated to the base line by plotting points from the descending limb on semilogarithmic paper, and then the extrapolation was replotted on the initial linear tracing. The area under the curve was determined with a compensating planimeter, and cardiac output was determined according to the formula,

$$F = \frac{Ceq. \times B.V.}{Cavg. \times t}$$

F represents flow; Ceq. is the final dilution; Cavg. is the average number of counts during time t;

B.V. is the blood volume; and t is the time of primary passage of indicator through the heart.[9,13,14] This method of estimating flow was not satisfactory when applied to grossly distorted curves.

The linear recordings were analyzed for appearance time (A.T.), build-up time (B.T.), disappearance time (D.T.), and D.T./B.T. ratio, according to the methods of Swan and associates[2] for arterial dye-dilution curves obtained by peripheral injection.

RESULTS

Inspection of the curves obtained from each group often demonstrated marked differences in contour. In the normal group the curves exhibited relatively rapid up- and downstroke (Fig. 1). If the flush was slow or poorly timed, the curve was spread out. So-called "double humped" curves, which were not infrequently obtained, offered difficulties in the analysis of their time components. Strict attention to the technique of injection, and positioning the probe according to the principles set forth by Pritchard and associates[9,10] appear necessary in order to obtain satisfactory results.

In patients with shunts, rapid upstrokes were usually seen, but the downstrokes were generally distorted, either by abnormally high recirculation humps or by relatively smooth but delayed clearance slopes (Figs. 2 and 3).

Analysis of Curves From Control Group.—Thirty-four curves from 22 normal subjects yielded the following mean values: (1) B.T. was 9.6 ± 2.7 seconds; (2) D.T. was 32.4 ± 10.2 seconds; (3) D.T./B.T. was 3.7 ± 1.8 (Table I). Appearance times (A.T.) were quite variable. Mean A.T. was 4.4 ± 3.4 seconds. The range of D.T./B.T. ratio was 1.5 to 7.9. Six of the 34 curves gave ratios greater than 5.0. The consistency of D.T./B.T. ratio in an individual was somewhat variable. In most individuals, repeated curves produced similar ratios, although in a few, greater variability was encountered. In one control subject, three successive studies gave ratios of 2.0, 4.2, and 7.3. Faulty technique may have caused such divergent results. Of the three probe positions used, none was deemed superior in the consistency with which satisfactory curves were obtained in this group.

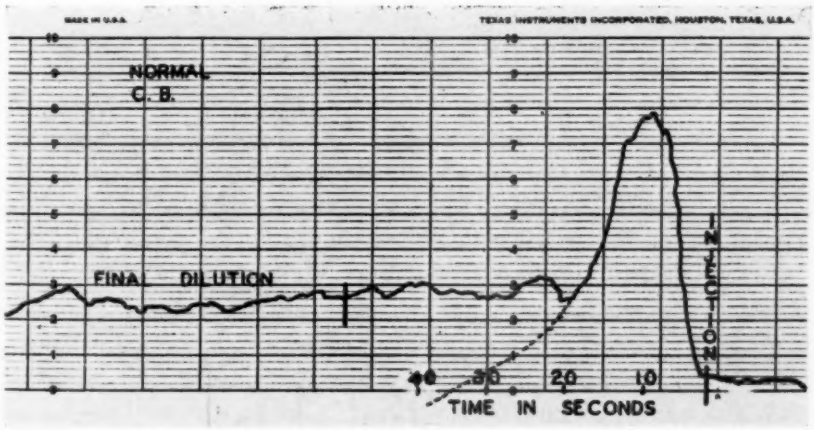

Fig. 1.—Precordial isotope-dilution curve obtained from a normal control patient The linear replot of the extrapolation is indicated by the dotted line. The vertical line along the recirculation slope indicates the end of the primary recording; final dilution was taken 10 minutes later. Note the steep downstroke, and that recirculation occurs at a point greater than halfway down the clearance slope.

TABLE I. ANALYSIS OF CURVES OBTAINED FROM SHUNT GROUP, TOGETHER WITH DIAGNOSIS, DIRECTION OF SHUNT, AND RATIO OF PULMONARY BLOOD FLOW TO SYSTEMIC BLOOD FLOW AS DETERMINED BY CARDIAC CATHETERIZATION (THE GROUP MEANS ARE COMPARED WITH THOSE FROM THE NORMAL GROUP)

DIAGNOSIS	DIRECTION OF SHUNT	PATIENT NUMBER	PROBE SITE	TIME (IN SECONDS) A.T.	B.T.	D.T.	D.T./B.T. RATIO	PBF:SBF RATIO
Patent ductus arteriosus	L-to-R	1.	4 LICS	1.0	6.0	40.0	6.7	1.3:1
		1.	Apex	4.5	6.5	36.0	5.5	1.3:1
		1.	2 LICS	3.0	6.0	41.0	6.8	1.3:1
		2.	Apex	3.0	6.5	43.5	6.7	2:1
		3.	Apex	4.0	6.0	72.5	12.1	2:1
		4.	4 LICS	3.0	11.3	55.3	4.9	1.4:1
		4.	Apex	5.0	7.0	52.5	7.5	1.4:1
		4.	2 LICS	2.5	9.5	55.5	5.8	1.4:1
Ventricular septal defect	L-to-R	5.	4 LICS	6.3	7.5	62.5	8.3	2:1
		6.	4 LICS	4.0	6.9	73.1	10.6	2.4:1
		6.	Apex	3.8	10.0	87.5	8.8	2.4:1
		7.	4 LICS	5.0	16.3	88.0	5.4	2.1:1
		7.	Apex	3.0	12.0	110.0	9.2	2.1:1
Interatrial septal defect	L-to-R	8.	—	3.5	4.0	50.0	12.5	2:1
		8.	—	3.5	5.5	38.5	7.0	2:1
		9.	4 LICS	2.5	7.5	87.5	11.7	>2:1
		10.	4 LICS	1.0	8.5	52.0	6.1	2.5:1
		10.	Apex	3.5	5.5	33.3	6.1	2.5:1
		10.	Apex	2.4	8.6	69.0	8.0	2.5:1
		11.*	—	18.0	22.0	148.0	6.7	2:1
		12.	4 LICS	0.8	4.3	30.0	7.0	1.5:1
		12.	Apex	1.0	5.5	23.0	4.3	1.5:1
		13.	Apex	1.3	8.0	76.0	9.5	3.3:1
		13.	Apex	1.3	8.0	71.0	8.9	3.3:1
		14.	Apex	3.5	12.5	60.4	4.8	2:1
		14.	Apex	7.0	13.1	76.9	5.9	2:1
IAD and VSD	L-to-R	15.	4 LICS	3.0	7.0	63.0	9.0	3:1
		15.	Apex	5.0	6.0	57.5	9.6	3:1
IAD and total anomalous pulmonary venous drainage	L-to-R R-to-L	16.	4 LICS	3.0	4.5	62.0	13.8	1.5:1
		16.	2 LICS	3.0	12.0	85.0	7.1	1.5:1
Pentalogy of Fallot	R-to-L L-to-R	17.	2 LICS	3.5	11.5	62.5	5.4	0.75:1
		17.	Apex	6.0	11.5	37.5	3.3	0.75:1
Aortic septal defect	L-to-R R-to-L	18.	2 LICS	7.0	5.5	42.5	7.7	—
Tricuspid atresia	R-to-L ?L-to-R	19.	Apex	0.5	7.0	63.0	9.0	0.5:1
19 Patients 34 Curves		Mean Values		3.8 ±3.0	8.5 ±3.7	61.9 ±24.8	8.0 ±2.9	
22 Normals 34 Curves		Mean Values		4.4 ±3.4	9.6 ±2.7	32.4 ±10.2	3.7 ±1.8	
		p Values		<.5>.4	<.2>.1	<.001	<.001	

*Semilog recorder
A.T.: Appearance Time. B.T.: Build-up Time. D.T.: Disappearance Time.
L-to-R: Left-to-right. R-to-L: Right-to-left.
IAD: Interatrial septal defect. VSD: Ventricular septal defect.

Analysis of Curves From Shunt Group.—Analysis of 34 curves obtained from the 19 patients with proved shunts yielded the following mean values: (1) B.T. was 8.5 ± 3.7 seconds; (2) D.T. was 61.9 ± 24.8 seconds; (3) D.T./B.T. was 8.0 ± 2.9 (Table I).

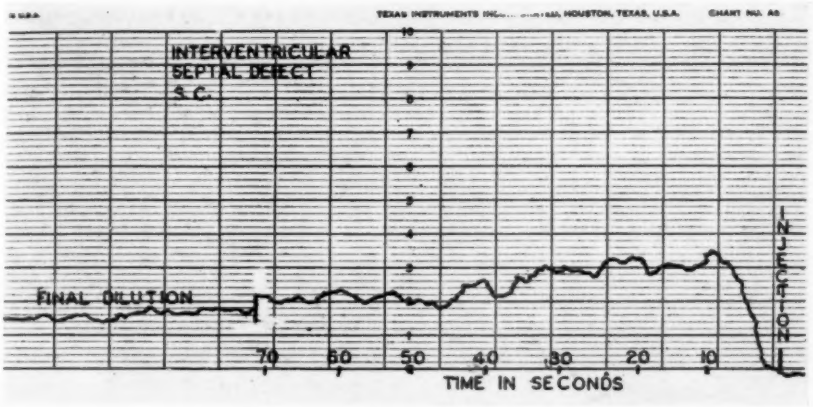

Fig. 2.—Precordial isotope-dilution curve from Patient 7 with probe at apex (see Table I for analysis). Note rapid upstroke and greatly delayed clearance, indicating abnormal central recirculation of RIHSA.

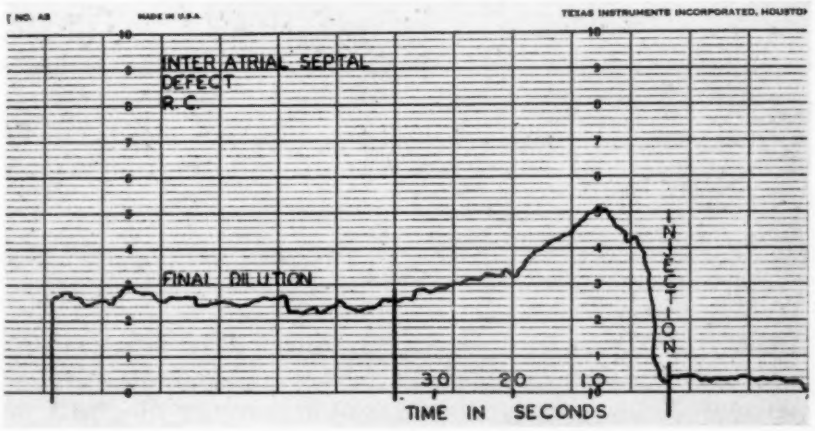

Fig. 3.—Precordial isotope-dilution curve from Patient 10 with probe at apex (see Table I for analysis).

Four curves obtained from 4 different patients (2 had interatrial septal defects, 1 had a patent ductus arteriosus, and 1 had pentalogy of Fallot) presented D.T./B.T. ratios of less than 5.0 (Fig. 4). Each of these patients, however, did demonstrate ratios that were over 5.0 on one or more additional studies. The differences in the mean values for D.T. and D.T./B.T. between the control and shunt groups were significant (p less than .001).

There did not appear to be a completely linear relationship between the PBF:SBF (pulmonary blood flow:systemic blood flow) ratio and the D.T./B.T. ratio, but there was less overlapping with the D.T./B.T. ratios obtained from the normal group in those patients with the highest PBF:SBF ratios (Fig. 5).

Although the group is a somewhat small one for the purpose of quantifying the sensitivity of this procedure, 12 curves were recorded in 5 patients with calculated PBF:SBF ratios of less than 1.5:1. Three of these 12 curves had D.T./B.T. values of less than 5.0. Although 9 of 12 curves in these 5 patients were considered to to be abnormal, 3 of the 4 "false negative" curves seen in the shunt group were in these patients in whom the volume of shunted blood was about one third or less of the total left ventricular output.

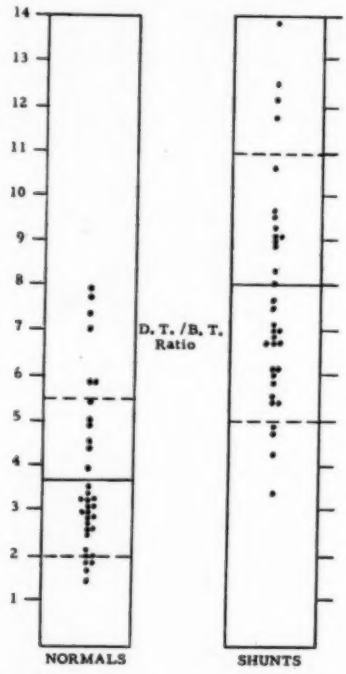

Fig. 4.—Each dot represents D.T./B.T. ratio of curves obtained in each group. Heavy line is mean of each group. Dotted lines represent limits of one standard deviation.

Appearance times were variable. They ranged from 0.5 second up to 7 seconds, save for one patient in whom the time was 18 seconds. Mean A.T. was 3.8 ± 3.0 seconds. No consistent differences in appearance time were correlated with the various sites upon which the probe was focused. This suggested that the bulk of the curves were mixed, i.e., more than one cardiac chamber contributed to the contour. Appearance time could not be relied upon to differentiate right-to-left shunts in the 4 cyanotic patients studied. One of 6 curves in this group did show an extra hump on the upstroke, which may have been caused by early appearance of isotope across the right-to-left shunt, or by early normal left heart contribution.

In patients with left-to-right shunts, various positions of the probe did not change the resultant D.T./B.T. ratio. Inspection of the curves did reveal the following points of interest: (1) Patients with left-to-right shunts due to interatrial or interventricular septal defects exhibited more obviously abnormal curves when the probe was focused over the fourth left intercostal space at the left sternal border, as compared with curves from the apex or second left inter-

costal space (abnormal recirculation occurred higher on the clearance slope). (2) Patients with left-to-right shunts across a patent ductus arteriosus tended to have less grossly abnormal curves when compared with patients who had interatrial or interventricular septal defects (abnormal recirculation occurred somewhat lower on the clearance slope), and focusing over the apex or second left intercostal space at the left sternal border brought out the abnormalities more efficiently than focusing over the fourth left intercostal space.

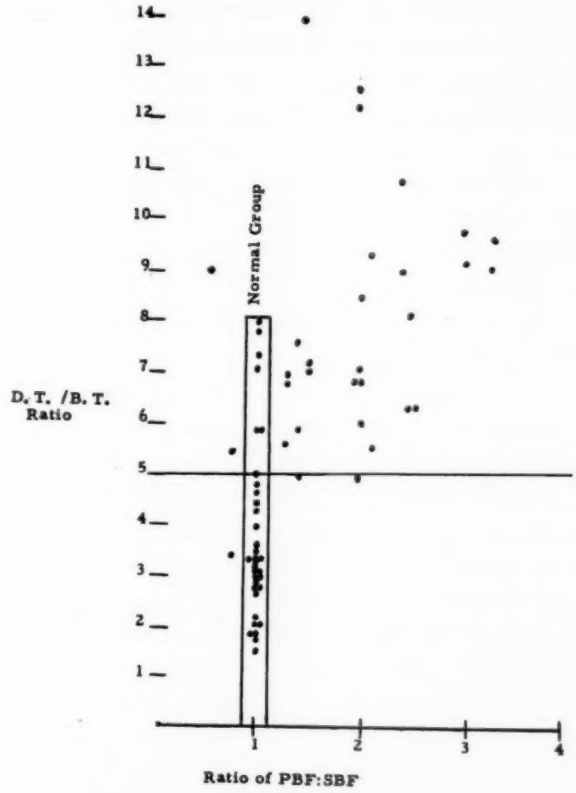

Fig. 5.—Graphic representation of the relationship between the D.T./B.T. ratio and the PBF:SBF ratio. Note that the D.T./B.T. ratio was not consistently related to the magnitude of shunt. There was less overlap with the normal group in those with the highest PBF:SBF ratios.

Comparisons were made between pulmonary and systemic flows determined according to the Fick principle from data obtained at catheterization and those arrived at by application of the modified Stewart-Hamilton formula noted above to the isotope-dilution curves. Agreement between these two methods was poor in the shunt group. Attempts to partition the curves by extrapolating the first portion of the descent (before recirculation) in order to get a more nearly accurate estimate of the primary curve were unsuccessful. This may have been due, in part, to lack of an adequate number of points for accurate extrapolation. Although this formula yields reliable flow estimates from normal curves, it does not therefore seem applicable to grossly distorted curves obtained from shunt patients.

DISCUSSION

This study demonstrates that externally monitored isotope-dilution curves may often confirm the suspected presence of left-to-right shunts at the atrial, ventricular, and pulmonary arterial levels. The technique requires only a venipuncture and extremely small doses of RIHSA.

When curves were normal or nearly normal in contour, acceptable estimates of cardiac output were obtained, but accurate flow data were not available from markedly abnormal curves by the methods employed. Application of the "forward triangle" method to these curves might be helpful in this regard.[24]

The specific area upon which the probe was focused did not appear to be a critical determinant of the D.T./B.T. ratios obtained in this series, but it would appear necessary to adhere to the principles outlined by Pritchard and associates,[9] in order to obtain reliable reflections of the pathways of flow through the heart and proximal great vessels.

Conditions other than intracardiac shunts may alter the contour of the precordial isotope-dilution curves. Slowing of all time components due to low cardiac output or increased volume has been observed by both arterial dye-dilution studies and precordial monitoring,[10,25-27] but normal D.T./B.T. ratios should be obtained from curves altered in this manner. Valvular regurgitation, however, disproportionately delays clearance of indicator in arterial dye-dilution curves and would mimic left-to-right shunt curves analyzed by the methods employed in the present study.[26-29] The few precordial isotope-dilution studies performed in this laboratory on patients with congestive failure or severe mitral insufficiency are in agreement with these observations. Caution should be observed in the interpretation of precordial curves from those patients who may have left-to-right shunts *and* regurgitant lesions (endocardial cushion deformities with mitral or tricuspid insufficiency, or associated functional regurgitation secondary to ventricular dilatation), inasmuch as delay in clearance of indicator may be produced by either of these abnormalities alone.

Final opinion concerning the detection of right-to-left shunts cannot be drawn from the data summarized here. It would appear that the method of Greenspan and associates,[19] in which simultaneous appearance curves were obtained from the precordium and femoral artery, will be superior to precordial curves alone. The left-to-right shunts in cyanotic patients were consistently demonstrated (Fig. 6). Variability of appearance time and upstroke anomalies were present because the probe was, during the recording of most curves, actually "seeing" more than one ventricle when positioned at the apex, and at the second left intercostal space, both aorta and pulmonary artery were in view. Thus, the initial portions could have been produced by either side of the heart, and would not allow the differentiation of early appearing indicator. Abnormal left-to-right shunting was readily noted in the delayed fall of the downslope in most cases when large amounts were present. This method was sensitive enough to pick up shunts representing approximately 25 per cent of the left ventricular output in the majority of instances. The data on patients with smaller shunts was too scant to exactly quantify the limitations of the technique.

The somewhat irregular nature of the isotope-dilution curves contrasts with the more familiar arterial dye-dilution curves. Aside from the nonbiologic technical vagaries of the detection equipment, it may be that some of these irregularities reflect such phenomena as heterogeneous mixing of isotope, changes in relative distance between probe and heart due to respiration, variations in stroke output and central blood volume, and flow through blood vessels between the probe and the cardiac cavities. Indeed, some interesting attempts at estimating coronary blood flow by means of precordial monitoring have already been made.[30] These irregularities do not detract from the over-all contour, provided that appropriate attention is paid to injection procedure and position of the probe. Distinct, diagnostic differences are readily seen when curves obtained from persons without shunts are compared with those obtained from patients with left-to-right shunts of significant magnitude.

Preliminary work underway in the authors' laboratory indicates that the use of a 2-inch crystal with flat-field collimation provides a considerable increase in sensitivity. This allows the recording of much smoother curves, since the count rate meter may be set at 30,000 to 100,000 c.p.m., and the time constant at 0.5 second while employing smaller doses of RIHSA for the count rates. Studies performed thus far with this equipment are in general agreement with the results reported herein.

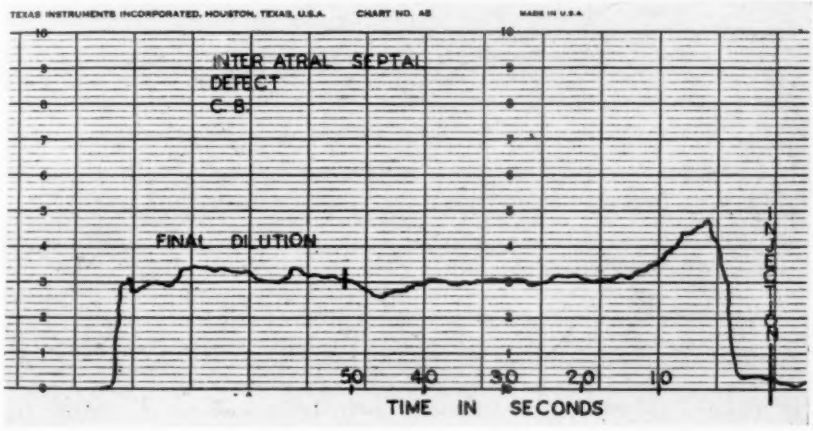

Fig. 6.—Precordial isotope-dilution curve from Patient 16, who had bidirectional shunting. The delayed clearance indicates left-to-right shunting, but neither appearance time nor shape of upstroke is indicative of the right-to-left shunting.

SUMMARY

Precordial isotope-dilution curves were recorded and analyzed in a series of normal patients and in a group of patients in whom intracardiac shunts were demonstrated by means of cardiac catheterization. It was readily possible to distinguish most patients with left-to-right shunts by simple inspection of the resultant curves as well as determination of the disappearance time/build-up time ratios. Right-to-left shunts were not detected in this study.

Application of this simple method might be useful in large screening clinics.

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Evidence That Serum Potassium Is Not the Etiological Agent in Ventricular Fibrillation Following Coronary Artery Occlusion

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In 1839, Blake[1] injected potassium carbonate into the jugular vein of dogs and observed that the animals died within 45 seconds after the injection. He concluded that death was the result of the direct action of potassium on the heart. In 1883, Ringer[2] reported the interrelationships of sodium, potassium, and calcium on the contractions of the heart of the frog and noted failure of the heartbeat when a potassium solution was used alone. In 1895, Langendorf[3] demonstrated on the mammalian heart that potassium was a heart poison and caused cardiac arrest. Wide acceptance was gained for the concept of "potassium inhibition," in which arrest of the heart in diastole occurs when the heart is perfused by fluid containing a higher than normal concentration of potassium or abnormally low concentration of calcium and normal concentration of potassium. Support for the effect of potassium on the heart was provided by work from many laboratories in the years that followed, and in 1956, Effler and co-workers[4] used potassium citrate to produce temporary cardiac arrest during cardiac surgery in man. On the other hand, an arrhythmia which simulates ventricular fibrillation has been reported to occur after the intravenous injections of potassium in doses smaller than those necessary to produce cardiac arrest. Such "paradoxical action of potassium," although first observed in 1864, was studied and clarified by Wiggers[5] in 1930.

More recently, Harris and associates[6] attributed an excitant action to potassium in ventricular fibrillation complicating coronary artery ligation in dogs. In this report, an elevation of serum potassium in the blood draining the infarcted myocardium is postulated as acting as an excitant on the remaining normal myocardium, with the production of ventricular fibrillation. This point of view was supported by Cherbakoff and associates,[7,8] who sampled coronary sinus blood through a Cournand catheter. They correlated ventricular extrasystoles, tachycardia, and fibrillation which followed coronary artery ligation with rising levels of potassium in the coronary sinus blood. In animals pretreated

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with insulin and glucose or sodium bicarbonate, these phenomena were sometimes delayed. This delay was correlated with stable or low levels of potassium in the coronary sinus blood.

With recent increased use of potassium salts in the treatment of cardiac arrhythmias, especially those complicating digitalis toxicity (Lown and Levine,[9] Sampson and co-workers[10,11]) and states of potassium depletion, it was felt that an attempt to clarify or reconcile the inhibitory, paradoxical, and excitant actions of potassium would be of practical importance.

This report will deal with the results of 83 experiments on dogs in which various constituents of coronary sinus blood were studied after ligation of the left anterior descending coronary artery (LAD). Our results do not support an excitant role for potassium in ventricular fibrillation. It is the purpose of this report to present evidence that it is unnecessary to assume an excitant role for potassium in order to explain the observation of the elevated serum potassium in some cases of ventricular fibrillation in dogs. Such an assumption may misdirect therapeutic efforts to prevent or abolish this serious arrhythmia which is a common cause of death following coronary occlusion.

METHODS

1. Mongrel dogs under pentobarbital-sodium anesthesia were maintained on 95 per cent oxygen and 5 per cent carbon dioxide with an Emerson respirator. The heart was exposed through the right chest and the LAD dissected free from its accompanying vein. A ligature was placed around the LAD but not tied until control blood samples were drawn from the coronary sinus and the femoral artery.

2. Samples of blood from the coronary sinus were obtained by free flow without suction, through an indwelling polyethylene tube with a stainless steel obturator. The tube and obturator were inserted through an incision in the right atrium which was closed with a purse-string suture. The tube was inserted through the coronary sinus ostium for a distance of 4 to 5 cm. to prevent contamination with auricular blood. In some instances, a ligature was placed around the coronary sinus and tube after proper placement of the tube in the coronary sinus.

3. Serial electrocardiographic tracings were recorded throughout each experiment until the onset of ventricular fibrillation or until the end of the experimental period of 2 to 3 hours.

4. Concentrations of serum potassium were determined with a flame photometer.

5. Blood samples were drawn at various intervals after ligation of LAD from 1 minute to 3 hours. Experiments were terminated when ventricular fibrillation occurred, or if normal sinus rhythm was present for 2 to 3 hours after the ligation of LAD.

RESULTS

1. Ventricular Fibrillation and Cardiac Standstill After Coronary Artery Ligation.—A total of 83 successful ligations of a major coronary artery were performed. Of this number, 25 dogs (30 per cent) developed ventricular fibrillation during the period of observation, 3 (4 per cent) developed cardiac arrest, and 55 (66 per cent) maintained a normal sinus rhythm throughout the experimental period, which did not exceed 3 hours.

In 13 of the 25 experiments in which ventricular fibrillation occurred and in 1 of 3 experiments in which cardiac standstill developed, it was not possible to obtain adequate samples of coronary sinus blood after the coronary artery had been ligated. This failure in some instances was due to technical difficulties, and

in others to the very early onset of ventricular fibrillation. These experiments will not be considered further; thus, there was a total of 12 satisfactory experiments in which ventricular fibrillation occurred 1 to 30 minutes after major coronary artery ligation, and 2 in which cardiac standstill resulted 10 and 25 minutes after ligation.

TABLE I. TWENTY-THREE DOGS WITH SIGNIFICANT INCREASE IN POTASSIUM IN THE CORONARY SINUS AFTER CORONARY ARTERY LIGATION

DOG NUMBER	INCREASE IN CORONARY SINUS POTASSIUM (MEQ.)	INCREASE IN FEMORAL ARTERY POTASSIUM (MEQ.)	CARDIAC RHYTHM
4.	0.7	1.0	NSR
7.	0.9	1.1	NSR
8.	0.6	0.4	NSR
16.	0.5	0.1	NSR
17.	0.6	0.5	NSR
19.	0.6	0.6	NSR
21.	0.6	0.3	NSR
28.	1.1	1.6	NSR
32.	0.5	0.3	NSR
33.	1.3	0.3	Vent. Fib.
34.	1.3	1.4	NSR
35.	1.4	0.3	Vent. Fib.
50.	2.4	Decrease	Vent. Fib.
55.	1.1	1.4	NSR
60.	0.6	0.5	NSR
65.	3.5	2.5	NSR
66.	1.2	0.4	NSR
70.	0.5	1.3	NSR
73.	2.1	1.9	NSR
82.	0.6	0.2	NSR
91.	2.6	Decrease	Asystole
92.	2.3	3.4	Asystole
95.	1.4	0.8	NSR

2. *Changes in Coronary Sinus and Femoral Artery Serum Potassium After Coronary Artery Ligation.*—Only 23 of 69 animals (33 per cent) in which it was possible to obtain serial samples from the coronary sinus showed a significant increase in coronary sinus potassium of 0.5 mEq./liter or more. Thirteen of these 23 showed an increase in the concentration of potassium in the femoral artery, whereas 10 of these 23 showed no such increase. In 2 instances, a decrease in the concentration of potassium in the femoral artery was observed during the sampling period, which extended for a maximum of 3 hours (Table I).

3. *Twenty-Three Experiments With Elevation of Potassium in the Coronary Sinus After Coronary Artery Ligation.*—Eighteen (78 per cent) of the 23 animals which showed an elevation of potassium in the coronary sinus maintained normal sinus rhythm throughout the experiment (Table I and Fig. 1). Three (13 per cent) of the 23 which showed an elevation of potassium in the coronary sinus terminated in ventricular fibrillation, and these did not show a significant increase in the level of potassium in the femoral artery (Table I and Fig. 1). Two (9 per cent) terminated in cardiac standstill, and one of these showed a definite increase in potassium in the femoral artery of 3.4 mEq. above the control 1 minute before asystole.

4. *Forty-Six Experiments Without Elevation of Potassium in the Coronary Sinus After Coronary Artery Ligation.*—Thirty-seven (80 per cent) of the 46 animals which did not show an elevated level of potassium in the coronary sinus maintained normal sinus rhythm throughout the experimental period (Fig. 1). Nine (20 per cent) terminated in ventricular fibrillation (Fig. 1).

5. *Coronary Sinus Flow After Onset of Ventricular Fibrillation.*—In 5 animals a free flow of blood continued from the indwelling coronary sinus tube for 1 to 2 minutes after the onset of ventricular fibrillation. Two of these 5 animals showed an increase of 3.0 and 2.5 mEq./liter above control levels for the coronary sinus, 1 an increase of 0.4 mEq./liter, and the other 2 showed no change in potassium.

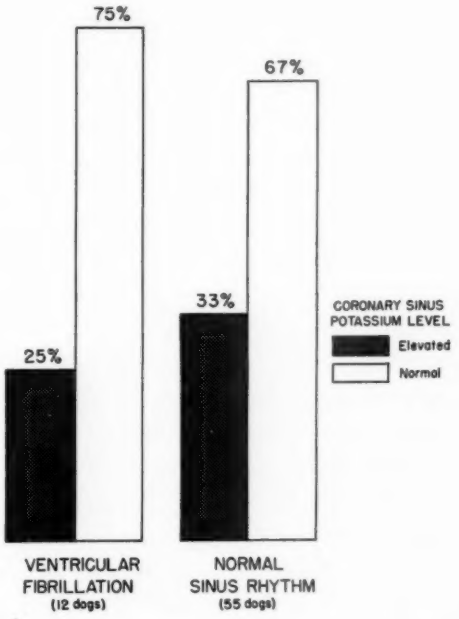

Fig. 1.—Lack of relationship between elevated levels of potassium in the coronary sinus and cardiac rhythm.

DISCUSSION

The occurrence of small but definite free flow from the coronary sinus for 1 to 2 minutes after the onset of ventricular fibrillation was a surprising finding. Studies are under way to determine the cause of this flow of blood.

The elevation of potassium in the femoral artery which was observed in some experiments was probably the result of a combination of causes. Potassium lost from damaged myocardial cells[12,16] may have contributed to the total intravascular pool of potassium. In addition, tissue anoxia secondary to hemodynamic disturbances which resulted from the myocardial infarction may have caused a loss of potassium from skeletal muscle and other body tissue.[13-15]

In only 23 of 69 of our experiments (33 per cent) were we able to demonstrate an elevation of potassium in the coronary sinus blood following coronary artery ligation. This is contrary to claims of an increase in the potassium in coronary sinus blood reported in the literature.[6,7] Furthermore, only 3 (13 per cent) of

the animals which showed an elevated level of potassium in coronary sinus blood developed ventricular fibrillation, whereas 9 (20 per cent) animals which failed to show an elevation in potassium in coronary sinus blood developed ventricular fibrillation. Finally, 18 animals with an average elevation of 1 mEq./liter of potassium in coronary sinus blood maintained a normal sinus rhythm* throughout the experimental period. These results indicate that there is no consistent relationship between potassium in the coronary sinus or that in the femoral artery and ventricular fibrillation, and, therefore, the view that serum potassium is responsible for initiating fibrillation is not tenable. The elevation of potassium sometimes observed in coronary sinus blood most likely reflects the loss of potassium from the anoxic myocardial cells. Ability to demonstrate this shift in potassium would depend, therefore, on the adequacy of collateral circulation in flushing out the potassium lost from the damaged cells into the extracellular fluid and hence into the blood. Any arrhythmia observed under these conditions would more likely be related to the altered potassium gradient between the myocardial cells, depleted of potassium as a result of anoxia, and the interstitial fluid potassium, rather than to any direct stimulating or excitant action of potassium lost into the blood stream.[17,18] Infusion of potassium may produce effects similar to intracellular depletion of potassium by temporarily reducing the normal potassium gradient of 30:1 (intracellular potassium to extracellular potassium).

It is hoped that a more rational approach to the prevention and possibly the treatment of ventricular fibrillation will result from the clear realization that elevation of the level of potassium in coronary sinus blood, when observed after LAD ligation, is the result of myocardial depletion of potassium. This potassium is not the initiating factor of ventricular fibrillation complicating coronary artery occlusion, although the myocardial depletion of potassium may be. Therefore, therapeutic efforts should not be aimed at lowering serum potassium, but rather at seeking means to prevent loss of potassium from the myocardium or to shift potassium back into the myocardial cells.

SUMMARY

1. Elevation of the concentration of potassium in the coronary sinus occurred only in 33 per cent of 69 dogs after ligation of a major coronary artery.

2. Eighteen of the 23 dogs (78 per cent) with an elevation of the level of potassium in the coronary sinus blood maintained a normal sinus rhythm throughout the experimental period.

3. Of 12 animals which developed ventricular fibrillation after coronary artery ligation, only 3 showed a significant elevation of the concentration of potassium in the coronary sinus. The other 9 failed to show any increase in the level of potassium in the coronary sinus. None of the 12 showed an increase in the concentration of potassium in the femoral artery.

4. These results fail to support the thesis that an increase in the levels of serum potassium incites ventricular fibrillation after coronary artery ligation.

*Occasional premature ventricular beats were observed early after ligation in many of the animals.

We wish to thank Mr. Doward B. Patterson, Jr., for his technical assistance in the performance of the blood analyses.

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Case Reports

Tetralogy of Fallot With Rheumatic Stenosis of the Aortic Valve

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The incidence of rheumatic valvulitis in patients with congenital heart disease is difficult to ascertain. In patients having congenitally bicuspid aortic valves, the incidence of all rheumatic infections of the heart has been variously reported from 16 to 62 per cent,[1,2] and in those with atrial septal defects it has been as high as 13 per cent.[3] Gelfman and Levine,[4] in examining 181 autopsy cases of congenital cardiac malformations, found 25 (14 per cent) in which there was evidence of superimposed rheumatic infection. One was a patient with tetralogy of Fallot but no details were given as to the specific rheumatic lesion in the heart. Since their study, little has been written concerning the occurrence of rheumatic heart disease in patients with congenital defects.

A patient recently studied at the National Heart Institute was shown to have the tetralogy of Fallot and calcific aortic stenosis of rheumatic origin. To our knowledge, no description of a patient with these combined lesions has been recorded, and in view of the sparsity of information on the subject a description of the clinical, hemodynamic, and anatomic findings in this patient was considered worth while.

CASE REPORT

F. P. (No. 02-10-20), a 25-year-old female student, was admitted to the National Heart Institute on Aug. 17, 1958. Cyanosis and a heart murmur were known to have been present since birth. She had always had exertional dyspnea and was said to have squatted to rest during childhood. The history also revealed that at 4, 7, and 12 years of age she had had attakcs of joint effusions with pain associated with fever and an elevated erythrocyte sedimentation rate. On each occasion the diagnosis of acute rheumatic fever was made and she was hospitalized. The patient's dyspnea was more severe after the last such illness. Ten years prior to admission an attempt had been made, at another hospital, to perform a right subclavian–pulmonary artery anastomosis but the procedure was abandoned because of the small size of the right pulmonary artery. She had remained on almost complete bed rest for 10 years, and for the 2 months immediately prior to admission had been hospitalized because of marked dyspnea.

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Physical examination revealed the patient to be well developed and slightly obese; there was marked generalized cyanosis. The blood pressure was 106/75 mm. Hg and the pulse 104. A healed right posterolateral thoracotomy incision was present. A left ventricular tap and a pronounced right ventricular lift were palpable over the precordium. A Grade 4/6 ejection type of systolic murmur was audible over the entire precordium but was maximal at the base of the heart and was transmitted to the carotid vessels. A Grade 2/6 murmur was also present over the entire thorax during diastole, and the two murmurs were considered to be continuous. There was a single second heart sound at the base. Normal sinus rhythm was present and the peripheral arterial pulsations were normal. There was marked clubbing and cyanosis of all digits.

Routine laboratory examinations were normal except that the hemoglobin was elevated to 22.8 Gm. per 100 ml. and the hematocrit was 69 per cent. Fluoroscopic and radiographic examinations revealed right ventricular enlargement, decreased pulmonary vascularity, and calcification in the region of the aortic valve (Fig. 1). The electrocardiogram demonstrated right axis deviation, right atrial enlargement, and right ventricular hypertrophy.

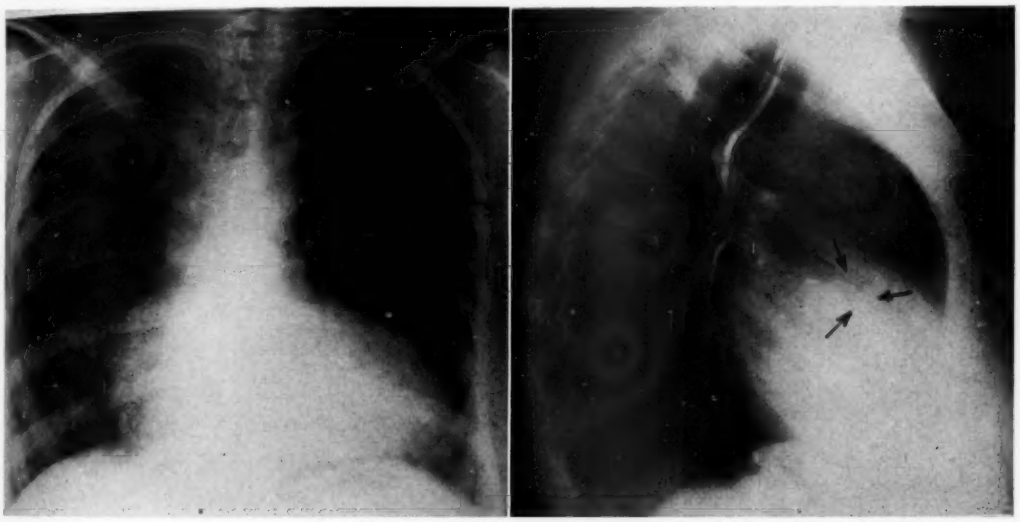

Fig. 1.—Posterior-anterior (*A*) and lateral (*B*) projections of the chest x-ray. The heart is grossly enlarged, particularly the right ventricle, and no main pulmonary artery is visible. Pulmonary vascularity is decreased. The ring of calcification in the region of the aortic valve is indicated by arrows in the lateral view.

Right heart catheterization was carried out on Aug. 18, 1958. The pressure in the right ventricle was 160/5 mm. Hg, and in the brachial artery it was 90/63 mm. Hg. Arterial indicator-dilution curves recorded after right atrial and right ventricular injection revealed a large right-to-left shunt which originated from the right ventricle. The peripheral arterial saturation was 61 per cent. The nitrous-oxide index[5] was 0 per cent in the right atrium and 100 per cent in the right ventricle; the latter value indicated that the catheter had sampled left ventricular blood immediately beneath the aortic valve. The catheter could not be manipulated into the pulmonary artery or aorta.

A selective angiocardiogram with right ventricular injection revealed a large ventricular septal defect and a large single vessel arising from the base of the heart (Fig. 2). Two ventricles were demonstrated but the pulmonary arteries were never opacified. The angiocardiographic findings were thought to indicate pulmonary atresia (pseudotruncus arteriosus) or a severe form of tetralogy of Fallot. Since the ventricles were functioning with a common ejectile force, the systolic pressure gradient of 70 mm. Hg between the right ventricle and brachial artery indicated the presence of associated aortic stenosis. To confirm this diagnosis and to localize the site of outflow obstruction, a retrograde arterial catheterization was performed. The catheter entered

the left ventricle from the aorta, and the pressures recorded as it was withdrawn across the aortic valve proved the presence of valvular aortic stenosis (Fig. 3).

Because of the severe deformity of the right ventricular outflow tract and the absence of pulmonary arterial opacification demonstrated by the angiocardiogram, the patient's lesions were not considered to be amenable to complete correction. Therefore, a systemic pulmonary anastomosis and aortic valvulotomy were decided upon. At the time of operation it was clear that the congenital lesion was a severe form of the tetralogy of Fallot; there was marked dextroposition of the aorta, and the main pulmonary artery was hypoplastic. There was an intense systolic thrill in the ascending aorta, which was dilated. The left pulmonary artery was small, but it was possible to perform an anastomosis between the end of the left subclavian artery and the side of the left pulmonary artery. After the anastomosis had been opened, an aortic valvulotomy was carried out by closed transventricular dilatation. Measurements of ventricular and systemic arterial pressures before and after the valvulotomy revealed almost complete abolition of the pressure gradient across the aortic valve. In the immediate postoperative period the patient was hypotensive and refractory to the administration of blood and vasopressor agents. Approximately 2½ hours after the conclusion of the operation, cardiac arrest occurred and resuscitation was unsuccessful.

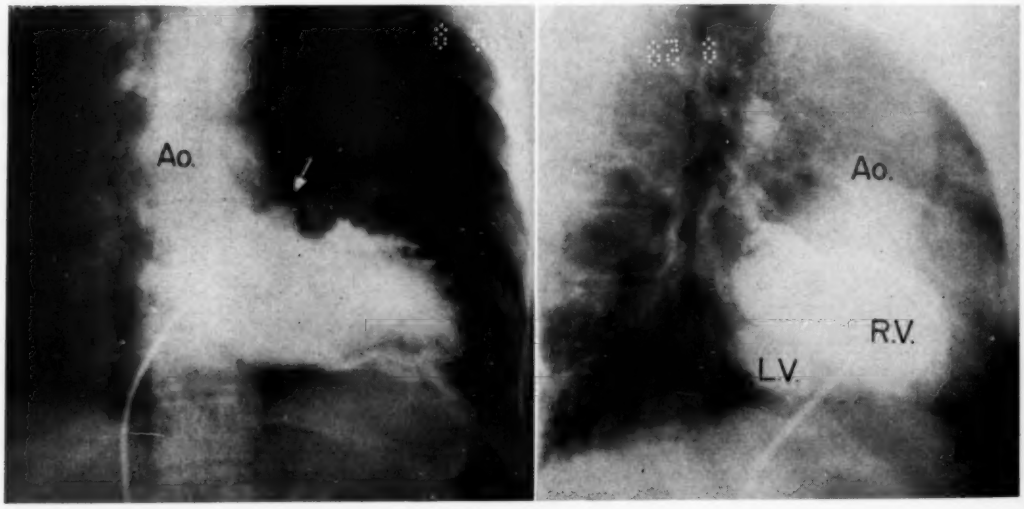

Fig. 2.—Anteroposterior (*A*) and lateral (*B*) views of the selective angiocardiogram. The injection was made into the right ventricle. Both the right ventricle (*RV*) and left ventricle (*LV*) are filled, and the dilated aorta (*Ao*) is seen in both views. The outflow tract of the right ventricle appears to end blindly (arrow), and the pulmonary arteries do not fill.

Pathologic Findings.—The heart weighed 700 grams, there was hypertrophy of both ventricles, and the ventricular cavities were small. There was severe stenosis of the right ventricular infundibulum, which was due to myocardial and endocardial thickening; the opening in the outflow was only 1 cm. in diameter. The pulmonic valve had three cusps, was stenotic as well as hypoplastic, and measured 3 cm. in circumference. The subclavian–pulmonary artery anastomosis was patent. A defect in the membranous portion of the ventricular septum was present; the mitral ring was calcified. The aorta was dextroposed, and there was dilatation of the ascending aorta. The aortic valve had three normally situated cusps. There was marked calcification of the aortic annulus and cusps, and there were numerous calcific deposits on the aortic side of the leaflets and to a lesser extent on their ventricular side (Fig. 4). The valve had little or no mobility. The right and left coronary cusps were fused near the ring; the other commissures showed evidence of having been recently opened.

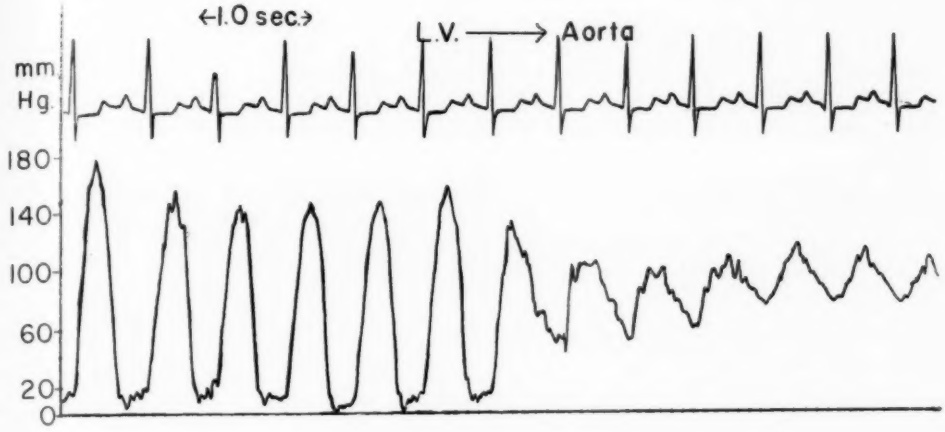

Fig. 3.—Pressures recorded during retrograde arterial catheterization as the catheter was withdrawn from the left ventricle into the aorta. A peak systolic gradient of 40 to 50 mm. Hg is evident. The patient was anesthetized during this study.

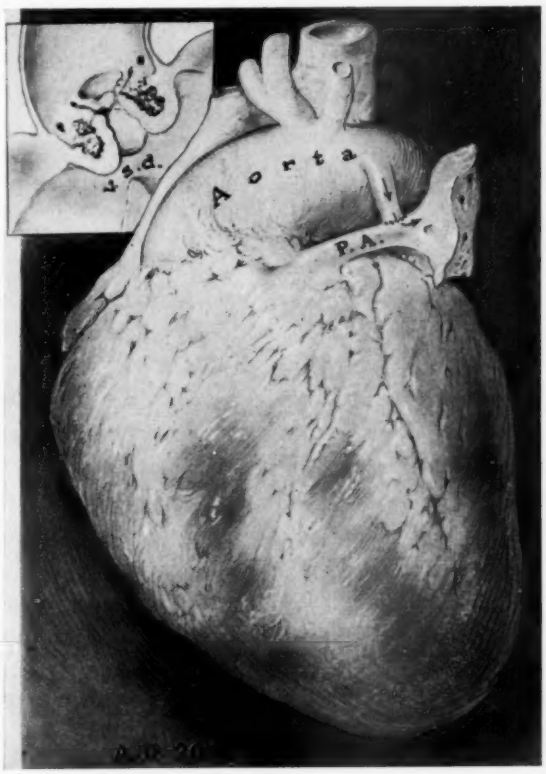

Fig. 4.—The appearance of the heart and great vessels at autopsy. The dextroposition of the aorta and the diminutive main and left pulmonary arteries are shown. The site of the patent left subclavian–pulmonary anastomosis and the extreme dilatation of the aorta are also evident. The relations of the calcified aortic valve to the ventricular septum are shown in the insert.

Microscopic examination of the aortic valve showed it to be greatly thickened and to contain lobulated areas of calcium surrounded by dense fibrous tissue and focally dense chronic inflammatory cellular infiltrates (Fig. 5). The valve was prominently vascularized. Other histologic examinations revealed that the mitral valve was thickened and there was fibrous tissue as well as many thick-walled vessels deep in its substance. There were widely scattered focal areas of scarring in the myocardium of both ventricles and extensive endocardial calcification.

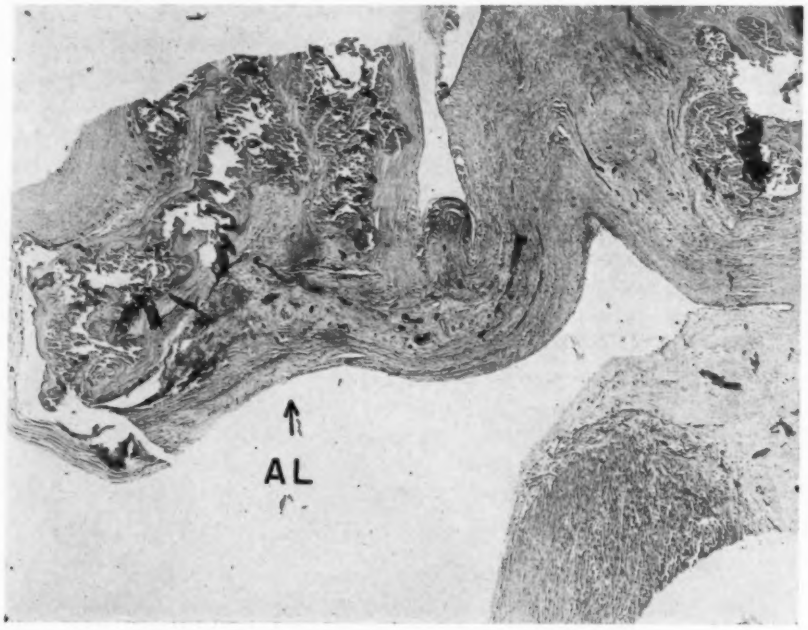

Fig. 5.—Photomicrograph of a vertical section through an aortic leaflet. The leaflet (*AL*) is extensively infiltrated with fibrous tissue and chronic inflammatory cells. The clear areas represent sites in which calcium was present. Numerous vascular channels are evident in the base of the leaflet. (Hematoxylin and eosin; ×14, reduced ⅙.)

COMMENT

There can be little doubt regarding the cause of the aortic stenosis in this patient. The episodes of acute rheumatic fever were well documented and the presence of chronic inflammation in both the mitral and aortic valves provided anatomic proof of rheumatic disease. There was nothing to suggest a congenital deformity of the aortic valve. Because of the combination of defects in this patient, there were unusual problems in diagnosis and treatment. Since the main pulmonary artery and its branches did not opacify in the selective angiocardiogram, it was concluded preoperatively that the congenital lesion was probably pulmonary atresia. It may be difficult to distinguish this malformation from the severe forms of tetralogy of Fallot. A large portion of the pulmonary blood flow in this patient was undoubtedly from systemic arterial collaterals; these were probably responsible for the continuous murmur heard over most of the thorax.

In the presence of a large ventricular septal defect, as in this patient, the systolic pressures in the right ventricle, left ventricle, and aorta are ordinarily equal. However, the systolic pressure gradient between the right ventricle and brachial artery indicated the presence of obstruction, which was subsequently

proved to be at the aortic valve. Since the usual anatomic defects of the tetralogy of Fallot were present in addition to the aortic stenosis, there was obstruction to the outflow of blood from both ventricles. An increased burden on the left ventricle was produced in much the same manner, but to a lesser degree, as in the right ventricle. It seems likely, also, that blood flow through the hypoplastic right ventricular outflow tract and small pulmonary artery was increased somewhat by the abnormally high ventricular pressure. It is clear, however, that there was an added work load on the right ventricle besides that which resulted from the pulmonic stenosis, because the presence of aortic stenosis further increased the resistance to right ventricular ejection. The degree of anatomic narrowing of the aortic valve in this patient, if present as an isolated lesion, would not have been considered alarming, but since it represented obstruction to the only route of emptying for both ventricles, it assumed greater significance. Since the aorta was receiving all the blood from the left ventricle and most of that from the right, the flow across the valve was greatly increased and a larger aortic gradient was present in this patient than would have been present in a patient having isolated aortic stenosis with the same degree of anatomic narrowing.

When surgical treatment for this patient was considered, a completely corrective procedure was thought not to be feasible because of the hypoplastic right ventricular outflow tract and pulmonary arteries. The creation of an artificial ductus alone would have increased the burden on the left ventricle by increasing the return of blood to the left side of the heart. A similar situation is seen following the construction of an anastomosis in patients with tetralogy of Fallot in whom the outflow of blood from the left ventricle is impeded by extreme dextroposition of the aorta. Relief of the aortic stenosis, in this patient, would be expected to relieve the excess workload of both ventricles; it is doubtful whether a reduction in ventricular pressure would have significantly decreased the flow of blood through the pulmonary artery after the anastomosis was opened. The cause of death in the immediate postoperative period was most likely related to the poor myocardial function which certainly accompanied the myocardial fibrosis she was shown to have.

SUMMARY

A patient is described in whom a severe form of the tetralogy of Fallot was complicated by rheumatic stenosis of the aortic valve. These diagnoses were established by the clinical findings and the results of right and left heart catheterization and selective angiocardiography. An aortic valvulotomy and subclavian–pulmonary anastomosis were carried out, but the patient died in the immediate postoperative period. The pathologic findings are described and a discussion of the hemodynamic alterations which accompanied this unusual combination of defects is presented.

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Evidence in Support of the Neoplastic Nature of Cardiac Myxoma

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Primary neoplasms of the heart are rare, being observed by Straus and Merliss[1] in only 0.0017 per cent of 480,000 autopsies. A wide variety of mesenchymal tumors of cardiac origin have been described, including rhabdomyoma, lipoma, vascular tumors, fibroma, neurofibroma, granular cell myoblastoma, fibroelastic hamartoma, and myxoma.[2] Whether many of these represent true neoplastic growths has been the subject of considerable controversy. The myxoma represents the most frequent tumor of the heart, and is considered to account for approximately 50 per cent of the reported cases.[3] More than 200 examples have been recorded. The majority of these have been observed in persons who were 30 to 60 years of age, although examples have been noted in patients who were from 3 months to 68 years of age. No conclusive evidence indicating the predilection for either sex has been presented. In approximately 75 per cent of the cases the myxoma has been present within the left atrium, particularly at the fossa ovalis. Less frequent sites are the right atrium[4] and left ventricle.[5] In the case reported by Nichols,[6] bilateral atrial myxomas were encountered. Although the myxoma may be an incidental finding at necropsy, clinical manifestations referable to valvular obstruction, obstruction to atrial outflow, or embolic phenomena may be manifest more frequently.[7] Classic clinical features such as digitalis-resistant cardiac failure associated with arrhythmias and adventitious cardiac sounds are unexplained. The latter frequently vary periodically as well as with change in position. These features have frequently led to an erroneous clinical diagnosis of rheumatic heart disease. However, with the recent advent of cardiac angiography and catheterization, premortem diagnosis is more frequent. Diagnosis appears imperative since advances in cardiac surgery have allowed for the successful extirpation of such lesions in approximately 10 instances.[8] Although the clinical course exhibited by patients with cardiac myxoma may be relatively rapid, Strouse[9] has observed a patient with such a lesion for 43 years.

Despite the documentation of the clinical manifestations and macroscopic features of the cardiac myxoma, there is no unanimity of opinion concerning its histogenesis or precise nosologic position. The most widely held considerations on

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the nature of this lesion are that it represents either a true neoplastic growth or is the result of an organized blood clot of the atrial or valvular endocardium. Less frequently mentioned concepts are those suggesting its hamartomatous nature or origin from blood vessels.[10]

The purpose of this report is to describe the clinical and pathologic features of a myxoma occurring in the left atrium of a 25-year-old man. The results of histologic and histochemical studies of this lesion and the comparison with thrombi, examples of degenerative verrucal endocardiosis, and excrescences of Llambl, neoplastic myxomas of other sites, and the fossa ovalis from infantile and adult hearts which appear to be normal have led to conclusions indicating its neoplastic nature.

CASE REPORT

The patient, a 25-year-old white man, was in good health until 2 years prior to death, at which time, while in the Army, he experienced syncope. He was unconscious for about 15 minutes, and upon awakening had mild weakness of the extremities.

Physical examination at that time was considered to be normal. However, while he was in the hospital, apical systolic and late diastolic murmurs were heard. Chest x-ray films disclosed minimal cardiomegaly. An electrocardiogram revealed rs in Lead I, qRs in Leads II, III, and aV_F, and qr in Lead aV_R, with normal precordial leads. He developed a termperature of 104°F., myalgia, and cough. A chest roentgenogram revealed a patchy infiltrate in the right lower lung. Sputum examination was negative for acid-fast or other pathogenic organisms. Venous pressure was 140 mm. of saline, and an arm-to-tongue circulation time was 29 seconds. Blood cultures, lupus erythematosus preparations, heterophil test, antistreptolysin-O titer, and serologic examination as well as hemogram and urinalyses were not remarkable. He became afebrile after the administration of penicillin.

Three months later he developed intermittent dyspnea and multiple ventricular premature beats. He was given a mercurial diuretic and lost 7 pounds. Quinidine and digitalis were also administered but the latter was discontinued because of the onset of bigeminal rhythm. He received 30 mg. of prednisone daily because of a tentative diagnosis of rheumatic myocarditis. He soon became asymptomatic and all medication was withdrawn. One month later he was transferred to another hospital for further evaluation.

At this time he developed acute pulmonary edema which responded to the rapid administration of digitalis and morphine. Examination at that time revealed the heart to be enlarged to the anterior axillary line. The pulmonic second sound was increased, and apical systolic and mid-diastolic murmurs were present. The right ventricle appeared to be enlarged, and the left atrium questionably so by fluoroscopy. Roentgenographic examination of the chest showed congestion and small effusions bilaterally. Other laboratory data were considered to be within normal limits. An electrocardiogram at that time revealed right axis deviation and a large R wave in Lead aV_R. Several consultants did not consider the patient to have mitral disease, and cardiac catheterization was suggested. However, the patient experienced syncope or an aura of such an event with sudden changes in position. He developed dyspnea and atrial flutter despite digitalis. Four days prior to death he experienced pain in the abdomen and extremities. He became distended and expired suddenly.

Autopsy Findings.—The body was well developed. Each pleural cavity contained 2,000 ml. of clear yellow fluid. The liver was large, extending 4.0 cm. beneath the right costochondral junction.

Lungs: Each lung weighed 600 grams. The cut surfaces exuded a blood-stained frothy fluid. Several hilar lymph nodes were partly replaced by homogeneous white tissue.

Heart: The heart weighed 550 grams. One third of the pericardial cavity was obliterated by fibrous adhesions. The left ventricle was markedly dilated but the other chambers only moderately so. A soft, pedunculated, yellow-pink mass with a bosselated surface, measuring 5.0 by 5.0 by 3.0 cm., occupied at least two thirds of the left atrial cavity (Fig. 1). One third of the mass was noted

to extend into the mitral orifice in situ. The base of this lesion was attached to the endocardium over the foramen ovale, which was anatomically closed. The atrial appendages were free of clots. The valves and chordae tendineae appeared to be normal. The right ventricle measured 0.3 cm., and the left measured 1.2 cm., in thickness. The posterior and lateral aspects of the left ventricle, including the apex, contained irregular areas of dense white tissue. The overlying endocardium was white and opaque. The coronary arteries were elastic.

Spleen, liver, gastrointestinal tract, and kidneys: These organs appeared to be congested. In addition, the cortices of the kidneys contained depressed, white areas.

Fig. 1.—Myxoma occupying major portion of left atrium. Extension into mitral orifice is evident.

Microscopic Findings.—

Heart: The atrial mass appeared in routinely prepared hematoxylin and eosin stained sections of Zenker's fixed tissue to be comprised principally of a relatively acellular mass of myxomatous material (Fig. 2). Moderate numbers of capillaries were evident within the myxomatous tissue. Cellular elements were represented by scattered solitary, large fusiform and stellate cells with large nuclei and abundant eosinophilic cytoplasm as well as short cords of somewhat similar-appearing, plump spindle cells (Fig. 3). Foci of hemosiderin deposition and clumps of more fibrillary, eosinophilic, acellular material were noted throughout the lesion. The outer surface was covered by large endothelial cells which were apparently contiguous with adjacent endocardial endothelium. A layer of elastic fibers, visualized in sections stained by the Verhoeff technique, was also evident at the periphery (Fig. 4). The base of the lesion contained a few larger blood vessels with well-formed medial coats and scattered deposits of calcium. The underlying endocardium disclosed a similar myxomatous change, and large blood vessels in this region frequently contained deposits of similar material within the intima, completelv surrounding the centrally placed lumens (Fig. 5). The media was often thinned. Other sections of heart revealed areas of myocardial fibrosis. Two small arteries in adjacent areas contained myxomatous material occluding the lumens (Fig. 6).

Lymph node: A fibrocaseous nodule which contained histoplasma capsulatum, as revealed in sections stained by the Grocott method, was evident.

Liver: Sections of liver revealed hemorrhagic central necrosis and inversion of the normal hepatic lobular architecture.

Kidneys: Sections of the kidneys revealed areas of old infarction. In one section the lumen of an interlobular branch of the renal artery was occluded by a myxomatous mass.

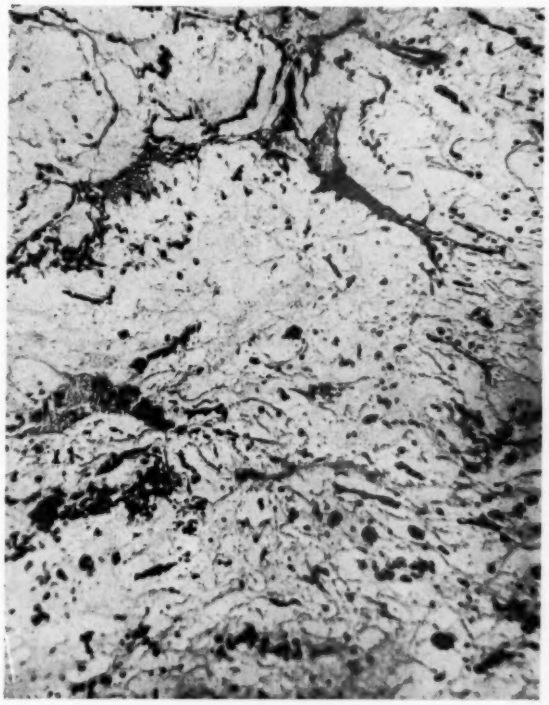

Fig. 2.—Appearance of major portion of cardiac myxoma revealing myxomatous tissue, capillaries and some calcification (appearing black) (× 100; reduced 1/3).

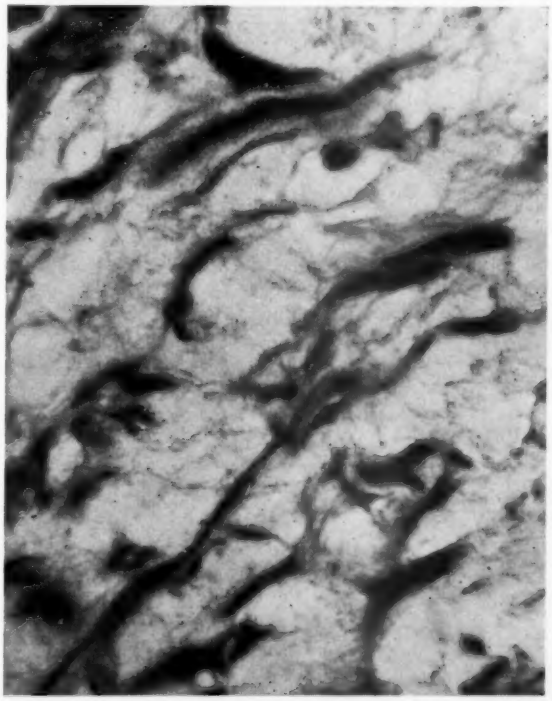

Fig. 3.—Cellular components of cardiac myxoma appear elongate and stellate. Polar processes are also evident (PTAH; ×900; reduced 1/3).

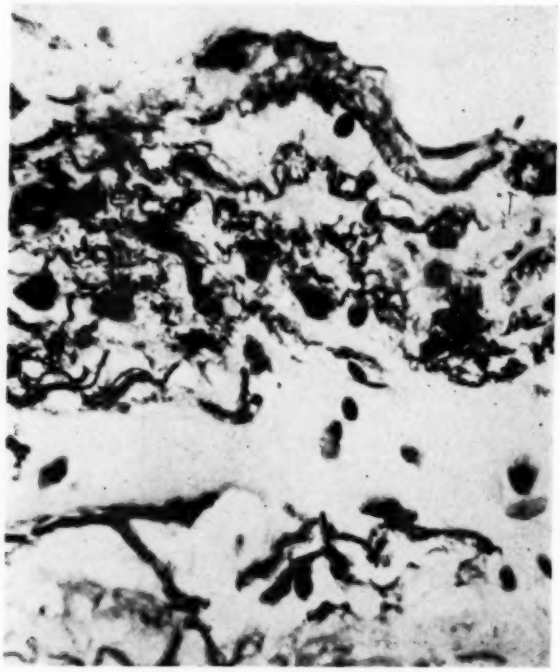

Fig. 4.—Periphery of cardiac myxoma containing elastic fibers (at top) (Verhoeff-van Gieson; ×440 reduced 1/3).

Fig. 5.—Myxomatous change of intima of arteries at base of cardiac myxoma (×100; reduced 1/3).

Fig. 6.—Myxomatous embolus in branch of coronary artery. Endothelialization of embolus is evident (×100; reduced 1/3).

SPECIAL STUDY OF MYXOMATOUS LESION

Portions of the myxomatous lesion of the left atrium, uninvolved atrial endocardium, atria from 6 normal adult and infantile hearts, auricular thrombi in various stages of organization, valves exhibiting the lesion of degenerative verrucal endocardiosis and Llambl's excrescences, a dermal myxoma, and umbilical cord were fixed in Zenker's acetic fluid, 10 per cent neutral formalin, and 95 per cent alcohol. Sections were prepared in the usual manner after being imbedded in paraffin, except that alcohol-fixed tissues were eliminated from hydration procedures. These were stained simultaneously according to the following methods as described in Lillie's *Histopathologic Technic and Practical Histochemistry*,[11] unless otherwise indicated.

1. Thionin, 1:10,000, pH 4, for 1/2 hr. with and without antecedent treatment with testicular hyaluronidase. (Wyeth, 150 TRU/c.c., pH 5.5, in M/10 acetate buffer for 1 hr. at 37°C.)
2. Azure A with and without prior sulfation according to Windrum.[12]
3. Alcian blue technique of Mowry for acid mucopolysaccharides.
4. Rinehart, Abul-Haj technique for acid mucopolysaccharides.
5. Periodic acid–Schiff technique with and without antecedent diastase and trypsin digestions (0.1 per cent malt diastase, pH 6, in phosphate buffer for 1 hr. at 37°C. and trypsin 0.1 per cent Difco 1:250, pH 7.6, in phosphate buffer for 3 hr. at 37°C.).

6. Trichrome with fast green counterstain.
7. Perl's iron.
8. Phosphotungstic acid hematoxylin.
9. Wilder's reticulum technique.

The results of the tinctorial reactions are tabulated in Table I. The major portion of the atrial mass as well as umbilical cord and cutaneous myxoma were vividly colored by the Alcian blue and Rinehart, Abul-Haj reactions and exhibited gamma metachromasia, indicating its acid mucopolysaccharide nature (Fig. 7, *A* and *B*). These reactions were in large part inhibited by pretreatment with hyaluronidase and were best visualized in sections prepared from alcohol-fixed tissue. These reactions were negative in Zenker's fixed tissue, and only faintly positive in those prepared from tissue fixed in formalin. The periodic acid–Schiff reaction of the atrial mass was only moderately reactive in the major portion of the lesion, although areas of more intense reactivity were evident. These latter

TABLE I. TINCTORIAL REACTIONS FOR MUCOPOLYSACCHARIDE IN MYXOMAS, BLOOD CLOTS, NORMAL ENDOCARDIUM, AND VALVULAR LESIONS OF POSSIBLE ETIOLOGICAL SIGNIFICANCE

	THIONIN	HYALURONIDASE-THIONIN	ALCIAN BLUE	RINEHART-ABUL-HAJ	PAS	DIASTASE-PAS	TRYPSIN PAS
Cardial myxoma	++++	+	++++	++++	++*	++	++*
Cutaneous myxoma	++++	+	++++	++++	++	++	++
Umbilicus	++++	+	++++	++++	++	++	++
Adult endocardium over fossa ovalis	—	—	—	—	—	—	—
Infant endocardium over fossa ovalis	—	—	—	—	—	—	—
Degenerative verrucal endocardiosis	—	—	—	—	—	—	—
Llambl's excrescence	—	—	—	—	—	—	—
Organizing mural thrombus	++†	+†	++†	++†	++++	++++	±

*The lakes of fibrillary eosinophilic material in the cardiac myxoma were strongly PAS-positive, trypsin labile, and PTAH-positive (fibrin).

†Only at site of organization (base). Remainder negative.

corresponded to zones which were also cyanophilic with the phosphotungstic acid hematoxylin stain and were promptly digested by trypsin, which strongly suggested their fibrinous nature. On the other hand, the lesions of degenerative verrucal endocardiosis and excrescences of Llambl failed to exhibit the reactions for acid mucopolysaccharide. Elastic fibers were evident throughout the entire lesion of the former and only at the altered valvular endocardium of the latter. This pattern was unlike that noted with the atrial mass, in which such fibers had a peripheral distribution. The examples of organizing thrombus also revealed acid mucopolysaccharide. However, such material was limited to zones of granulation tissue and was absent in major portions of the clots or in those situations in which collagenization prevailed. Elastic fibers were inapparent in these clots.

The atrial endocardium immediately subtending the myxomatous lesion and the large blood vessels in this area revealed reactions similar to the main tumor mass. However, the endocardium of the fossa ovalis from normal adult and in-

A.

B.

Fig. 7.—Acid mucopolysaccharide as evidenced by a positive Alcian blue reaction (appearing black) in cardiac myxoma. *A*, Similar material is evident in the cutaneous myxoma; *B*, optically clear spaces represent shrinkage artefact (×200; reduced 1/3).

fantile hearts and the uninvolved endocardial areas in the heart of this patient failed to disclose these reactions. The only recognizable difference between the endocardium at the fossa ovalis and other atrial zones was an apparent increase in thickness of the former.

COMMENT

The clinical manifestations exhibited by this patient are similar to those emphasized in other recorded examples of this disorder and have been recounted previously in this report. Although a clinical similarity between atrial myxoma and mitral stenosis is recognized, it appears worthy of note that unlike the latter, atrial dilatation was slight in this as well as in many of the other recorded examples of myxoma. The possibility that the lack of dilatation in this instance may have been due to intermittent mitral obstruction is in keeping with the proposed ball-valve action of this lesion. Furthermore, its location in some instances suggests that obstruction of the ostia of the pulmonary veins may occur and in this manner inhibit dilatation of this chamber.

Although the cardiac myxoma morphologically resembles myxomas of other sites, there has been a reluctance to unequivocally accept its neoplastic nature. The frequency of such lesions in otherwise normal hearts, their predilection for the fossa ovalis, and the lack of definite evidence that a thrombus within the heart or elsewhere exhibits a comparable morphologic appearance in the course of its evolution argue against its thrombotic nature, a view first advocated by Bacmeister,[13] Thorel,[13] Karrenstein,[14] and Husten[14] in the early part of this century. More definitive evidence refuting the possibility that the myxoma results from alteration in a pre-existing thrombus is provided by the results of this study. The unique deposition of elastic fibers along the peripheral, free margin of the growth is unlike that observed in thrombi in which such structures are absent. This pattern in myxoma suggests a herniation of neoplastic elements into the cardiac lumen rather than a superficial deposition. Although it is most frequent to observe a varied chronologic appearance of emboli emanating from cardiac thrombi, the emboli in this instance were all of similar appearance, morphologically and tinctorially resembling the primary lesion. The presence of hemosiderin within the myxoma cannot be considered as evidence in support of its derivation from blood elements since it is most likely that episodes of hemorrhage from the frequent vascular channels within the lesion could give rise to such deposits. A similar explanation for the occasional deposits of fibrin encountered in the myxoma also appears tenable. The arrangements and morphologic appearance of the cellular elements of the myxoma are unlike those observed in thrombi, resembling those noted in other myxomas and umbilical cord.

The histochemical features of the myxoma in this case were identical to those observed in an umbilical cord and an example of cutaneous myxoma, all exhibiting positive reactions for acid mucopolysaccharide. It is of interest that the mesenchymal derivation of the former and neoplastic nature of the latter has not been questioned. Although acid mucopolysaccharide may be evident in the granulation tissue of thrombi at sites of early organization, such material is inapparent

when organization is complete and characterized by mature fibrous tissue. On the other hand, the acid mucopolysaccharide of the myxoma, which we, on the basis of the histochemical studies performed, have considered to be most likely of the sulfated and nonsulfated types,[15] represents the outstanding feature of all areas of the lesion. The results noted for the demonstration of acid mucopolysaccharide in the myxoma with the various fixatives employed may in large part explain inconsistencies apparent within the literature concerning the presence of such material (commonly alluded to as "mucin") within these lesions. Reactions for such material were strongly positive in sections prepared from tissue fixed in alcohol, only mildly so in those from formalin-fixed tissue, and negative in those from tissue prepared after Zenker's fixation. The lack of tinctorial and structural similarities between the cardiac myxoma and the lesions of degenerative verrucal endocardiosis and excrescences of Llambl preclude consideration of the latter as possible sources for such myxomatous lesions.

The foregoing evidence indicates the neoplastic nature of the cardiac myxoma. However, we have no convincing explanation for its most frequent site of predilection, the fossa ovalis. Although Kesserling[16] and Ribbert[17] suggested a possible derivation of the myxoma from myxoid rests at the fossa ovalis, the results of our study of a limited number of examples of normal hearts, and the study of Pritchard[3] on a much larger series, have failed to disclose such structures at this site. Although it has been suggested that the myxoma represents a hamartoma,[10] a tumor comprised of parts indigenous to a site without autonomous growth, the predilection for the manifestations of cardiac myxoma to appear between the fourth and seventh decade strongly suggests that its growth does not cease with the apparent attainment of cardiac maturity; thus, it would not fulfill an essential requirement for being designated as a hamartoma. Furthermore, our studies have failed to disclose myxomatous tissue in the normal heart at the fossa ovalis. The recognition of a morphologically and tinctorially similar alteration of arteries at the base of the myxoma in this case appears unique and worthy of note. Maun[18] depicted a similar alteration of vessels in a case of myxoma which he recorded and attributed to disuse atrophy. A precise interpretation of this change appears to be less apparent to us. We do not consider it to represent a tumor embolus because of its uniformly circumferential disposition beneath the vascular endothelium, which is unlike other tumor emboli observed. Whether this change is of histogenetic significance—being in this regard similar to the vascular concepts of the derivation of some leiomyomas—or represents vascular invasion by the neoplasm as occasionally observed in other neoplastic growths, or reflects a more general mesenchymal response to neoplastic growth cannot be stated with certainty but represent plausible considerations for further observations.

SUMMARY

The clinical and pathologic features of an example of atrial myxoma occurring in a 25-year-old man are presented. Histochemical study has revealed tinctorial similarities between this lesion and examples of cutaneous myxoma and umbilical cord: notably the presence of acid mucopolysaccharide of the sulfated

and nonsulfated types. On the other hand, similar material was not observed in atrial or other thrombi—except at the sites of early organization—or examples of degenerative verrucal endocardiosis of Llambl. Moreover, dissimilar morphologic characteristics were apparent in the myxoma and the latter lesions. Although these considerations indicate the neoplastic nature of the cardiac myxoma, no explanation for its site of predilection at the fossa ovalis is evident. Examination of the endocardium of this site in normal adult and infantile hearts has failed to disclose myxoid or other unusual tinctorial or morphologic abnormalities. Attention is directed to a myxomatous change in the arteries at the base of the atrial myxoma, and its possible role in histogenesis is discussed.

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Review

A Review of the Benzothiadiazine Derivatives in Relation to Cardiovascular Disease

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The benzothiadiazine derivatives have recently become prominent in this age of rapidly advancing therapeutic frontiers. In a short 2-year span they have revolutionized diuretic and antihypertensive therapy. In addition, the investigation of their action has served to clarify many aspects of electrolyte and water balance, and renal tubular function. Up to the present time, 6 different derivatives have been used clinically, with varying degrees of success. Because of the widespread interest in these drugs, a review of the benzothiadiazines seems indicated.

Since the development of sulfanilamide, it has been known that compounds with an unsubstituted sulfamyl group have some diuretic effects. Sulfanilamide, for example, produces diuresis by inhibition of carbonic anhydrase and resultant excretion of excess sodium and bicarbonate.[1-4] Roblin and associates[5] concentrated on sulfonamide derivatives in a search for saluretic diuretics of greater potency than the mercurials. They found the benzothiazole derivative to be an effective inhibitor of carbonic anhydrase in vitro, but an ineffective diuretic in vivo because it was too rapidly metabolized. Acetazoleamide,* 2-acetylamino-1, 3, 4-thiadiazole-5-sulfonamide, was found to be 300 times more active than sulfanilamide in its inhibition of carbonic anhydrase in vitro and to have a marked effect on electrolyte and water excretion.[6,7] This drug has been used as an effective diuretic, but the loss of bicarbonate which it induces tends to produce a hyperchloremic acidosis. Thus, it should only be used intermittently.

Sprague and his group systematically studied the diuretic properties of the sulfonamides.[8-12] They found unusual activity in the benzene-1, 3-disulfonamide series, which was enhanced by halogen, amino, or acylamino group substitution. When an acylamino group is located opposite the sulfamyl group,

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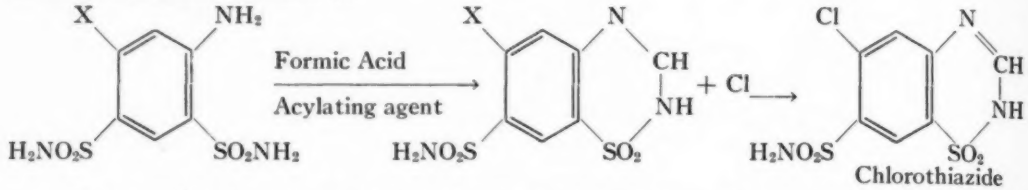
cyclization was easily obtained through the use of formic acid as the acylating agent. Among these cyclized compounds the greatest diuretic activity occurred with the substitution of Cl or Br in the 6 position. Using Cl as the halogen, the compound becomes 6-chloro-7-sulfamyl -1,2,4-benzothiadiazine-1, 1-dioxide, or chlorothiazide (Diuril*).

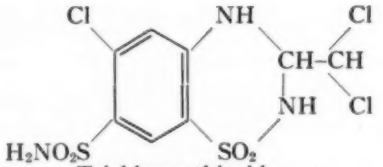


Chlorothiazide

This cyclized compound was found to have not only a marked natriuretic effect but also an equally marked chloruretic effect, and it was noted that this saluretic effect was considerably more marked than the carbonic-anhydrase inhibiting effect.[13,14] The compound was observed to be stable and excreted in the urine unchanged.

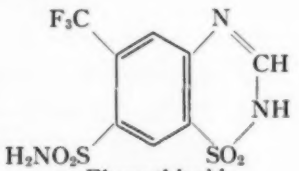
The addition of 2 H atoms to the unsaturated bond in the heterocyclic ring resulted in another active compound, 6-chloro-7-sulfamyl-3, 4-dihydro-1, 2, 4-benzothiadiazine-1, 1-dioxide, or hydrochlorothiazide (Hydrodiuril*, Esidrix†).[15]

The latest compound of the chlorothiazide group to be used clinically is trichlormethiazide‡ (Naqua).[16] This compound, 3-dichloromethyl-6-chloro-7-sulfamyl-3, 4-dihydro-1,2,4-benzothiadiazine-1, 1-dioxide, or dichloromethyl-chlorothiazide, is formed by the addition of a dichloromethyl group to the heterocyclic ring.

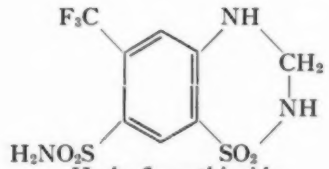


Trichlormethiazide

If the Cl atom is replaced by a trifluorinated methyl group, as was accomplished by Yale,[17] the compound becomes 6-(trifluoromethyl)-7-sulfamyl-2H-1, 2,4-benzothiadiazine-1, 1-dioxide, or flumethiazide (Ademol§). The addition of 2 H atoms to this compound forms 6-(trifluoromethyl)-7-sulfamyl-3,4-dihydro-2H-1, 2,4-benzothiadiazine-1, 1-dioxide, or hydroflumethiazide (Rontyl#) (Diademil§).[18,19]



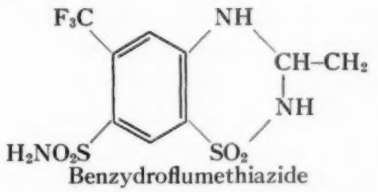
Flumethiazide



Hydroflumethiazide

*Merck Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia, Pa.
†Ciba Pharmaceutical Products, Inc., Summit, N. J.
‡Schering Corporation, Bloomfield, N. J.
§E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corp., New York, N. Y.
#Leo Pharmaceutical Products, Copenhagen, Denmark.

The attachment of a benzyl group to the heterocyclic ring produces 3-benzyl-6-(triflumomethyl)-7-sulfamyl-3, 4-dihydro-2H-1,2,4-benzothiadiazine-1, 1-dioxide, or benzydroflumethiazide (Naturetin§).[20]



Benzydroflumethiazide

Although the carbonic-anhydrase inhibiting ability of the benzothiadiazine derivatives was that function of these drugs which led to their development, it has become far less significant than the saluretic effect. In fact, the carbonic-anhydrase inhibiting effect is lowest and the saluretic effect greatest in the most recent and most potent derivatives (see Table I).[21]

The sequence in which the benzothiadiazine derivatives have been developed indicates to a large extent the amount of data, both pharmacological and clinical, which is available on each drug. Chlorothiazide has been studied much longer and more extensively than the others, whereas the latest addition, trichlormethiazide, has had the shortest period of observation. In this review, comparative studies and results will be mentioned wherever available, but the reader must be mindful of the fact that the experience with chlorothiazide is much greater than with the others.

TABLE I. CARBONIC-ANHYDRASE INHIBITION OF BENZOTHIADIAZINE DERIVATIVES

DRUG	RELATIVE MOLAR POTENCIES, SULFANILAMIDE = 1
Chlorothiazide	0.9–1.3
Flumethiazide	0.4–0.5
Hydroflumethiazide	0.09
Benzydroflumethiazide	0.08
Acetazoleamide	145–200

Report from the Pharmacology Division (Drug Metabolism), The Squibb Institute for Medical Research, July 22, 1959.

PHARMACODYNAMIC ACTIVITY

Absorption and Excretion.—The benzothiadiazine derivatives are absorbed rapidly from the gastrointestinal tract. They appear in the blood stream within 15 minutes and remain in significant concentrations for several hours.[14] Table II indicates relative plasma levels in dogs after the administration of equal doses of various thiadiazines.[21] These agents are excreted slowly by the kidney, and to a lesser extent by the liver. When they are administered orally, diuresis begins in 30 minutes and lasts at least 12 hours. When they are given intravenously, diuresis starts sooner but lasts only 2 hours. Therefore, these drugs are more suitable for oral than for intravenous administration.[14,22]

The thiadiazines are excreted both by glomerular filtration and by tubular secretion.[14,22-28] Chlorothiazide and probably its cogeners are eliminated by the proximal convoluted tubules in a manner similar to that of probenecid and p-aminohippurate. It would appear that probenecid and chlorothiazide compete for the same excretory enzyme systems, since the administration of probenecid diminishes the tubular excretion of chlorothiazide. Both compounds are related to tubular urate excretion, but have opposite excretory effects. Probenecid promotes urate excretion, whereas chlorothiazide diminishes it. This diminution apparently accounts for the elevation in serum uric acid found with the clinical use of the thiadiazines.[14]

TABLE II. PLASMA LEVELS AND EXCRETION OF THE BENZOTHIADIAZINE DERIVATIVES

DRUG (10 MG./KG.)	MEAN PLASMA LEVEL AT INTERVALS (MINUTES) AFTER ADMINISTRATION (μG/ML.)					PER CENT OF DOSE EXCRETED IN 24 HOURS
	30	45	60	90	120	
Chlorothiazide	3.8	4.2	4.2	3.0	1.4	55
Flumethiazide	3.8	3.9	2.8	2.0	1.0	60
Hydroflumethiazide	7.5	7.5	6.0	4.8	3.7	89
Benzydroflumethiazide	6.2	7.7	7.9	6.8	6.0	65

Report from the Pharmacology Division (Drug Metabolism), The Squibb Institute for Medical Research, July 22, 1959.

Effects on the Renal Tubule.—The principal therapeutic effect of the thiadiazine derivatives takes place in the renal tubule.[14,22-28] The drugs act at that portion of the proximal convoluted tubule where "free" water is released by selective solute reabsorption. By suppression of solute reabsorption, chlorothiazide causes excretion of large amounts of sodium and chloride in about equal proportions. Excretion of potassium is similarly increased to about half the amount of sodium, and excretion of bicarbonate is increased to about one quarter of the amount of chloride.[14,25] There is also some increase in the excretion of ammonia, but not until the second 12 hours, after maximum excretion of sodium has taken place.[25] Magnesiuresis has also been noted in some cases.[29,30]

Excretion of electrolytes varies with the individual thiadiazines. Chlorothiazide and flumethiazide produce similar excretory rates in the proportions noted above. Hydrochlorothiazide and hydroflumethiazide in smaller doses tend to produce a greater excretion of potassium and chloride than do the other cogeners, whereas benzydroflumethiazide and trichlormethiazide cause less excretion of potassium and only a minimal excretion of bicarbonate.[16,20,31]

Along with this profuse excretion of solutes there is a marked hypervoluria.[22-28] Repeated daily doses continue to be effective over an indefinite period of time, as long as body stores of sodium are not depleted.[14,22-28]

Plasma Electrolyte Changes.—Diuresis results in an initial lowering of plasma volume and a depletion of extracellular fluid.[32-34] Serum electrolytes, however, are

not disturbed appreciably.[35] Mild hyponatremia or hypochloremia may develop, but these are easily corrected by discontinuing the thiazide temporarily or increasing the dietary salt. Infrequently, a significant hypokalemia may occur,[23,24,32,36-46] particularly with the administration of hydrochlorothiazide or hydroflumethiazide.[47-50] The concomitant administration of steroids or the presence of cirrhosis of the liver tend to increase the likelihood of hypokalemia.[23,44,45,50-52] Rarely a hypochloremic, hypokalemic alkalosis may occur, which can be promptly relieved by oral potassium chloride.[23] Pre-existing forms of acidosis or alkalosis, however, are not aggravated by the administration of the thiadiazines.[14]

Renal Hemodynamics.—Although chlorothiazide acts primarily on the renal tubule, other less important effects occur proximal to this area. Renal plasma flow is inconsistently diminished, and glomerular filtration rate is consistently reduced in response to both oral and intravenous chlorothiazide. Serum osmolality is diminished, and blood urea nitrogen is increased.[34] Fortunately, these effects are not of sufficient magnitude to interfere with the saluretic properties of the drug.

Relation to Steroids.—Apparently, the thiadiazines do not exert their diuretic effect by aldosterone antagonism. Beyer[14] investigated this possibility by measuring adrenocorticosteroid activity after the administration of chlorothiazide. He found that there was no inhibition of steroids by chlorothiazide, and thus no aldosterone antagonism. Furthermore, the administration of spironolactone in the presence of chlorothiazide therapy causes an increase in natriuresis and diuresis.[53,54]

Comparative Potency.—The relative diuretic potency of the benzothiadiazine derivatives is presented in Table III.[16,20,55] The potency has been related to that of meralluride (intramuscularly), which is arbitrarily given a potency of 1.0. The oral mercurial, chlormerodrin, and the carbonic-anhydrase inhibitor, acetazoleamide, are included for comparison. It is evident that benzydroflumethiazide and trichlormethiazide are the most potent of the group. Hydrochlorothiazide and hydroflumethiazide are about equally more potent than meralluride, whereas chlorothiazide and flumethiazide are about equally less effective than meralluride.

TABLE III. COMPARISON OF POTENCY OF VARIOUS DIURETIC AGENTS

DRUG	ROUTE OF ADMINISTRATION	POTENCY ESTIMATION*
Benzydroflumethiazide	Oral	1.8
Trichlormethiazide	Oral	1.7†
Hydrochlorothiazide	Oral	1.4
Meralluride	Intramuscular	1.0
Chlorothiazide	Oral	0.8
Flumethiazide	Oral	0.7
Chlormerodrin	Oral	0.5
Acetazoleamide	Oral	0.25

*Ford, R. V., and Nickell, J.: Am. Heart J. 59:215, 1960.
†Ford, R. V.: Am. J. Cardiol. 5:407, 1960.

Antihypertensive Effect.—The benzothiadiazines were not used long before it was discovered by several investigators that they have an antihypertensive effect as well as a diuretic effect.[44,56-58] This discovery has opened a new therapeutic field of usefulness for these drugs. Many studies have been made of their antihypertensive activity. As a result, a controversy has arisen over the pharmacodynamics of their antihypertensive action. Two schools of thought have developed concerning this action. One school states that all of the hemodynamic effects related to the antihypertensive action of the thiadiazines are the results of natriuresis. The other school agrees that some of the hemodynamic effects are the result of natriuresis, but states that other hemodynamic effects require further explanation.

The first group of investigators[32,33,35,58-62] reasons in the following manner: natriuresis and diuresis result in a reduction in extracellular fluid space, plasma volume, and cardiac output, which in turn lowers blood pressure. Members of this school support their reasoning with a number of observations. (1) A marked reduction in the intake of salt has an antihypertensive effect. (2) The natriuresis and diuresis from intramuscular meralluride result in a temporary lowering of blood pressure. (3) The antihypertensive effect of a thiadiazine can be reversed by oral loading of salt (about 25 Gm. per day). Plasma volume will also be returned to normal in this manner.[35,63] (4) The intravenous infusion of dextran, in the presence of a thiadiazine antihypertensive effect, will produce a similar elevation in plasma volume and in blood pressure.[64] Some of these investigators reason further that the diminished responsiveness of the arteriole to norepinephrine in the presence of chlorothiazide[66,68] may be the result of the depletion of sodium in the arteriolar wall.[67-69] Some also believe that the increase demonstrated in peripheral resistance is an ineffective compensatory mechanism secondary to the reduction in plasma volume.[63,70] It has even been suggested that natriuresis followed by an increase in peripheral vascular resistance represents a shift from a saluretic component of essential hypertension to a neurogenic component of hypertension which is more susceptible to the effect of the centrally acting antihypertensive agents.[33,71] In some instances the thiadiazines will reduce blood pressure without diuresis or loss of weight. If the natriuretic theory of the antihypertensive effect of the thiadiazines is adhered to, some sort of inactivation or trapping of sodium must be postulated under these circumstances.[72]

The second school of thought,[53,54,73] which attributes only part of the antihypertensive effect of the thiadiazines to natriuresis, advances the following observations in support of its thesis. (1) Chlorothiazide does not reduce the blood pressure in normotensive individuals. (2) It produced diuresis without a reduction in blood pressure in normotensive individuals who were in congestive heart failure. (3) It reduces blood pressure in both compensated and decompensated hypertension. (4) It has a greater and more rapid effect on blood pressure than does salt restriction. (5) The antihypertensive effect of the thiadiazines is not always temporally related to the natriuretic and diuretic effect. (6) These agents continue to exert an antihypertensive effect when fluorohydrocortisone has counteracted the natriuretic effect of the thiadiazine. Conway and Lauwers[74] have observed in hypertensive individuals a return of plasma volume to normal

values and a reduction in peripheral vascular resistance below normal after more than 24 days of chlorothiazide therapy. These findings have been interpreted as evidence of a shift in the antihypertensive mechanism of chlorothiazide from that of natriuresis and a reduction in plasma volume to that of a reversal of increased arterial resistance. The cause for this change is unknown. These investigators suggest that it may represent a separate action of the drug or simply a readjustment of the increased peripheral resistance which occurred with the initial diuresis and hypovolemia. Freis[63] does not agree with these findings. His group has noted reduced volumes of plasma and extracellular fluid 8 to 12 months after initiation of chlorothiazide therapy and for as long as this therapy is continued.[64]

It is evident that further studies are required to settle some of these controversial points. Nevertheless, one cannot help but be impressed by the role of the investigation of thiadiazines in the elucidation of hypertensive mechanisms.

Antiarrhythmic Actions.—Chlorothiazide has been shown to have antiarrhythmic properties as well as diuretic and antihypertensive effects. Pines and associates[75] observed in dogs that the intravenous injection of chlorothiazide would abolish ventricular premature contractions and bigeminy produced by the injection of prednisolone phosphate. They also found that chlorothiazide had a similar but less definite effect on the premature contractions produced by intravenous strophanthin or digitalis glycosides. They were unable to explain the mechanism. DeNyse[76] noted the disappearance of arrhythmias in 6 patients on chlorothiazide. He attributed this phenomenon to general improvement in the cardiac status of the patients and not to any specific effect of the chlorothiazide.

CLINICAL EXPERIENCE

The benzothiadiazine derivatives have been successfully used as diuretics in various clinical states in which excess fluid has accumulated, such as congestive heart failure, nephrosis or the nephrotic stage of glomerulonephritis, cirrhosis of the liver, edema of pregnancy, and premenstrual edema. These drugs have also been used effectively in various hypertensive states, particularly in essential hypertension. The following discussion concerns their effectiveness in the clinical conditions related to the cardiovascular system.

Congestive Heart Failure.—The largest series of data on the clinical diuretic effectiveness of the benzothiadiazine derivatives has been accumulated in cases of congestive heart failure. Of course, a great preponderance of this data concerns the use of chlorothiazide. The diuretic effect of this drug has been reported in nearly 500 cases of congestive heart failure.[23,36-38,44,45,76-94] In approximately 86 per cent of the cases, 1 to 2 Gm. per day of chlorothiazide produced a satisfactory diuresis. (Loss of weight averaged 5 to 6 pounds in 24 hours.) Natriuresis varied from 37 to 380 mEq. of sodium per 24 hours in those cases in which it was measured. Chloruresis approximated natriuresis, and kaluresis averaged one half or less of the excretion of sodium. Hypokalemia did occur, but rarely created any symptoms. A number of instances of digitalis intoxication, however,

developed after the administration of chlorothiazide.[24,32,36,37,42-44] These were thought to result from kaluresis and hypokalemia. In general, those patients who were refractory to chlorothiazide were resistant to any form of diuresis. Only rarely did a patient refractory to chlorothiazide respond to meralluride intravenously. One investigator found that chlorothiazide could be made effective in refractory cases by administering it in small divided doses, 0.25 Gm. every 3 hours.[42,93]

Hydrochlorothiazide was found to be an effective diuretic in 211, or 92 per cent, of 230 cases of congestive heart failure.[46,48,50,51,95-106] Comparative studies by weight indicated that hydrochlorothiazide was 10 to 20 times as effective as chlorothiazide. Loss of weight and natriuresis were comparable, but kaluresis was somewhat more marked with hydrochlorothiazide than with chlorothiazide.[46,48,102,106] Therefore, hypokalemia and digitalis intoxication were more common with the former. Reports on clinical studies in which flumethiazide and hydroflumethiazide were used have been scant.[49,55,106-108] Most of the preliminary investigations have indicated that flumethiazide is comparable to chlorothiazide in dose and extent of activity, and that hydroflumethiazide is similarly comparable to hydrochlorothiazide. Published data are beginning to accumulate on the use of benzydroflumethiazide in congestive heart failure.[20,49,106-120] Sixty-six cases have been reported so far, with satisfactory diuresis in 65. The one patient who did not respond to benzydroflumethiazide was also unresponsive to other diuretics. As noted above, benzydroflumethiazide seemed to induce less kaluresis and thus be less likely to produce hypokalemia. CMR-807 has been shown to be a satisfactory diuretic in 10 cases of congestive heart failure.[16]

One group of investigators found that chlorothiazide improved the status of patients in congestive heart failure to such an extent that digitalis could be discontinued.[72] Other authors have shown also that digitalis could be safely discontinued in selected cases of congestive heart failure in which there was a regular sinus rhythm.[121]

Steroid Therapy.—Occasionally, one of the steroids is a necessary adjunct in the treatment of rheumatic carditis, the postcommissurotomy syndrome, or unrelated diseases in the presence of congestive heart failure. The incidence of sodium and fluid retention with the newer steroid analogs which are currently in use is lower than that with the older agents. Nevertheless, the incidence of fluid retention with steroid therapy is still sufficient to necessitate the availability of adequate diuresis. Each of the benzothiadiazine derivatives has been used successfully for this purpose.[20,79,80,98,114,117] Again, case reports are scanty but show uniformly satisfactory results.

Angina Pectoris.—Marshall[122] observed the alleviation of angina pectoris in 25 patients given chlorothiazide for diuresis. The degree of relief from chest pain seemed to be proportionate to the extent of diuresis. Thus, it was presumed that the beneficial effect of chlorothiazide resulted from its ability to reduce blood volume, and the work of an overburdened heart. Two other investigators have noted the disappearance of angina pectoris with the diuresis produced by chlorothiazide in congestive heart failure.[76,87]

Hypertension.—The benzothiadiazine derivatives have proved to be effective agents in the treatment of hypertension. Many studies have been made of the antihypertensive effects of these drugs both alone and in combination with other antihypertensive agents. However, these studies have been performed and reported in such a variety of ways that it is difficult to relate one study to another. Some investigators have reported blood pressure response in each case, whereas others have reported mean blood pressure response in a group of cases. Some have used placebo controls, whereas others have used no medication or other medication controls. Only a few have used a double-blind technique.

From the data at hand, it was possible to compile 645 cases in which courses of chlorothiazide had been given for varying periods of time.[32,35,39-41,46,62,67,72,123-140] Three hundred seventy-six of these cases, or 58.3 per cent, had a fall in blood pressure of at least 10 per cent or at least 10 mm. Hg in the diastolic pressure. Where mean blood pressures for a group of patients were reported, chlorothiazide produced a drop in the mean pressure in each instance. The placebo-controlled studies did not show as much of a fall in blood pressure as did the studies comparing a period of no medication with a period of chlorothiazide therapy.

Striking results have been obtained not with chlorothiazide alone, but with chlorothiazide in combination with other antihypertensive agents. The addition of Rauwolfia serpentina or its alkaloid, reserpine, to chlorothiazide reduced the blood pressure of 110 of 190 patients.[32,40,41,123-125,136] Hydralazine added to chlorothiazide decreased blood pressure satisfactorily in 47 of 66 patients.[32,40,123] The combination of chlorothiazide and the ganglion-blocking agents has uniformly given the most marked lowering of blood pressure, even in patients with severe hypertension. Of 299 patients, 273 showed a satisfactory blood pressure response, and in half of these cases the ganglion-blocking agent could be reduced in dosage or even replaced by hydralazine, veratrum, or rauwolfia.[32,35,40,41,46,62,123-126,137,139,140] In fact, this combination of antihypertensive medication has such a high incidence of orthostatic hypotension as a side effect that a word of caution is necessary. When chlorothiazide is added to a ganglion-blocking agent, the dose of the ganglion-blocking agent should be cut in half before chlorothiazide is started. Furthermore, chlorothiazide should be started in small doses (250 mg., b.i.d.) and gradually increased.

Consistently good results with chlorothiazide therapy have occurred in patients who have had a previous splanchnicectomy. Chlorothiazide administered to 46 patients who had undergone splanchnicectomy produced a satisfactory reduction in blood pressure in 42 cases.[35,73,132,140]

The antihypertensive effect of the other benzothiadiazine derivatives has been similar to that of chlorothiazide. When used alone they have been somewhat more successful than chlorothiazide. Hydrochlorothiazide produced a satisfactory lowering of blood pressure in 97 of 116 patients[48,83,97,98,101,102,141-143]; flumethiazide induced good response in 37 of 46 patients[144-146]; hydroflumethiazide lowered blood pressure in 21 of 31 patients[49,147]; and benzydroflumethiazide reduced blood pressure in 105 of 117 patients.[31,49,118,147-149] Evidently, the best results seem to have been obtained with benzydroflumethiazide. The experience with CMR-807 suggests a similar response, but the number of cases is too small

to properly evaluate the drug at present.[16] The cogeners of chlorothiazide also appear to have produced satisfactory results when combined with other antihypertensive agents; although the number of cases reported is still too few to tabulate.[31,83,141,144,146]

Toxic Effects.—Toxic effects associated with the benzothiadiazine derivatives have been reported infrequently. These agents have been implicated in the deaths of 4 patients. Johnston and Cornish[150] reported 4 cases of acute pancreatitis in patients taking chlorothiazide, 1 of whom died. This patient was a 78-year-old woman with severe arteriosclerotic heart disease, whose congestive heart failure was controlled with digitalis and chlorothiazide. She had been on this therapeutic regimen for 3 months when she developed acute pancreatitis, from which she died. Postmortem examination showed a severe hemorrhagic pancreatitis with extensive fat necrosis. The biliary tract was normal. The cause of the pancreatitis was not evident. The occurrence of acute pancreatitis in 4 patients on chlorothiazide who showed no evidence of biliary-tract disease, pancreatic tumor, infection or injury, or alcoholism made these investigators suggest chlorothiazide as a possible cause. The other 3 deaths, reported by Reinhardt,[41] show less association with chlorothiazide. One died of coronary thrombosis, one of salt-losing nephritis, and one of a low-salt syndrome. Undoubtedly, the last 2 cases were made worse by the natriuretic effect of chlorothiazide; but this is hardly a toxic effect of the drug. No deaths have been reported with the other thiadiazine agents.

The hematopoietic system has not been affected seriously by the benzothiadiazine derivatives, although 12 cases of purpura have been reported recently, 11 from chlorothiazide and 1 from hydrochlorothiazide.[131,151-155] In each case the purpura disappeared upon withdrawal of the drug. The Subcommittee on Blood Dyscrasias of the American Medical Association Council on Drugs[156] has reported 2 more cases of thrombocytopenia and 1 case of leukopenia in which chlorothiazide was the only drug implicated, and 1 case of pancytopenia, 5 cases of thrombocytopenia, and 2 cases of leukopenia in which chlorothiazide and one or more other drugs may have been implicated. There have been no hematological deaths reported from the benzothiadiazine derivatives.

The most common toxic reaction to these drugs is a maculopapular skin rash, which, according to Moyer and Beem,[46] occurs in about 1.5 per cent of the patients treated with chlorothiazide. The rash disappears when the drug is withdrawn. One case of exfoliative dermatitis associated with chlorothiazide has been reported by Dinon and associates.[43] Alopecia areata was noted in one patient.[157] One case of jaundice incident to the use of chlorothiazide has been reported by Drerup and associates.[158]

One other indirect toxic effect of the thiadiazine agents needs emphasis. The kaluretic and hypokalemic effect of these drugs not infrequently results in digitalis intoxication in those patients who are given concomitant digitalis therapy.[24,32,36,37,42-49] This effect is promptly relieved by the administration of potassium chloride. One patient who was not on digitalis developed ventricular bigeminy along with a marked increase in peripheral vascular resistance.[88]

Side Effects.—The side effects incident to the use of the benzothiadiazine derivatives are few and mild. Most of the resulting symptoms appear to be related to a disturbance of electrolyte or to gastrointestinal irritation. Lassitude, weakness, and vertigo, which have been noted with chlorothiazide and hydrochlorothiazide, have usually disappeared when the dose was lowered or potassium added. These symptoms have been somewhat less noticeable with benzydroflumethiazide. Anorexia, nausea, vomiting, heartburn, cramps, diarrhea, and constipation have all been observed.[36,39,41,42,44,46,96,97,100,115-117,141] Usually the symptoms have disappeared with continuation of the agent. Only rarely was it necessary to stop the drug to relieve the symptom. A few patients have complained of paresthesias or a reduced libido.[54]

One other group of side effects has occurred without symptoms. Hypokalemia, already mentioned, has been quite common, especially with hydrochlorothiazide and hydroflumethiazide.[23,24,32,36-46,47-50] It is reversed by the addition of potassium chloride. An occasional case of hypochloremic, hypokalemic alkalosis has been observed.[23] This abnormality also has been corrected by the administration of potassium salts. Hyponatremia has occurred, but has been rare, unless dietary salt was markedly restricted.[36,77] The addition of salt or the omission of the thiadiazine for 2 days a week has relieved this imbalance.

A gradual elevation in serum uric acid during thiazide therapy has been a common observation.[23,37,43,49,50,87,114,159-161] Normal levels of serum uric acid have risen above normal, and abnormal levels have become higher. One investigator has reported pain in the joints of the feet of 3 patients, 1 of whom had x-ray evidence of gout. Although elevated serum uric acid is common, symptomatic gout has been observed in only a few cases.[114,159,161,163,164]

Retention of nitrogen is the other important side effect of these agents. Elevations in blood urea nitrogen to a minor degree have been noted frequently in patients with normal kidneys. Much more important, however, is the fact that patients with renal disease and pre-existing retention of nitrogen will have a further increase in this retention, sometimes to an alarming degree (90 mg. per cent).[44,48,49,51,83,93,112,143,157] Two patients whose blood urea nitrogen was above 90 mg. per cent prior to therapy died during benzydroflumethiazide therapy.[157] Therefore, caution should be used in treating patients in whom there is nitrogen retention.

There are a few reports of elevated blood sugar incident to the use of these drugs.[49,63,97,129,162,165] These patients are considered to be preclinical diabetics whose diabetes is simply uncovered by the thiadiazines. The mechanism of this hyperglycemic effect is unknown. Such a reaction is rare, and reversible with discontinuation of the thiadiazine.[165]

COMMENT

It is evident that the benzothiadiazine derivatives have provided a marked advance in diuretic and antihypertensive therapy. Not only has their development been richly rewarding in clinical medicine, but it has also stimulated further investigation of the basic mechanisms of diuresis and hypertension. Many questions have been raised and some answered.

All of the benzothiadiazine derivatives are satisfactory therapeutic agents, with little to recommend one over the other, although preliminary data suggest that the 3-benzyl derivative of hydroflumethiazide may be slightly more effective than the rest. These drugs are satisfactory saluretics for short-term or intermittent use, and yet are equally suitable for continuous, long-term therapy. They tend to equalize rather than exaggerate electrolyte and acid-base imbalance, with the exception of hypokalemia and hypochloremic, hypokalemic alkalosis.

Only a few precautions are necessary in the administration of the benzothiadiazine derivatives: (1) Dietary sodium should not be severely restricted, so as to prevent hyponatremia. (2) The usual dietary content of potassium is sufficient to prevent hypokalemia in all but those patients receiving concomitant digitalis or steroid therapy, or in patients who have cirrhosis of the liver. Under these circumstances supplementary oral potassium is required. (3) Caution should be used in those cases in which thiadiazine therapy seems indicated in the presence of nitrogen retention. (4) As with any new drug, the clinician must be constantly alert for hepatic or hematopoietic reactions, even though these appear to be extremely uncommon.

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Annotations

Recurrence of Symptoms Following Mitral Valvulotomy

Mitral valvulotomy is firmly established as effective therapy for mitral stenosis when mechanical obstruction is the major physiologic defect. Approximately 70 per cent of well-selected patients can be expected to have subjective improvement after this procedure. It is becoming apparent, however, that improvement is often not sustained at its initial level. In a large series of patients who were followed up for 2 to 9 years by Ellis and associates,[1] 30 per cent of those who were initially improved for at least 1 year showed subsequent deterioration, and a recent series reported upon from Russia has shown similar results.[2] The patients who were followed up postoperatively by Bruce and his colleagues[3] have shown a perceptible diminution in the physical fitness index during the third year after operation.

There are multiple reasons for progressive cardiac disability after mitral valvulotomy. In the series studied by Ellis[1] the percentage of mitral insufficiency found or produced at operation, and the percentage of technically unsatisfactory operations were higher among those who showed deterioration than among those who maintained improvement. However, the fact that many patients with mitral insufficiency or unsatisfactory procedures did maintain improvement indicates these are not the only factors associated with deterioration. Recurrent rheumatic fever was suspected in some of the patients. Restenosis of the valve undoubtedly occurs, but seems to be, after 10 years of experience with valvulotomy, a relatively rare phenomenon when a technically satisfactory operation has been performed. Restenosis is certainly much more rare than recurrence of symptoms.

Hemodynamic data obtained after valvulotomy have been helpful in understanding the recurrence of symptoms in some patients. Resting pulmonary arterial and wedge pressures are usually significantly reduced by valvulotomy, but these pressures may rise strikingly with exercise.[4,5] This is often true even in patients who have experienced excellent symptomatic results. Left heart catheterization[6,7] usually reveals a reduction in the pressure gradient across the mitral valve, but this gradient is seldom abolished. The studies of Donald and co-workers[4] indicate that cardiac output in relation to oxygen consumption remains below normal, both at rest and during exercise. Thus, it appears that valvulotomy even when successful in relieving symptoms does not necessarily restore normal hemodynamics. As long as the heart and lungs continue to function under an increased pressure load, progressive disability in some patients is to be expected.

It is extremely important to differentiate patients with recurrence of symptoms due to restenosis who may be improved by additional surgery from those with recurrence of symptoms due to mitral insufficiency, rheumatic myocarditis, or the progression of cardiac disease due to abnormal hemodynamics despite a "surgically" satisfactory valvulotomy. Left heart catheterization with demonstration of a significant gradient across the mitral valve is the most satisfactory method available for identifying cases of restenosis. For this purpose, base-line studies of the mitral gradient shortly after valvulotomy would be extremely valuable; however, the risk of this procedure must be considered in relation to the frequency of the problem of restenosis of the valve.

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The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy: Correlation With the Anatomic Findings

The ability to diagnose right ventricular hypertrophy (RVH) from the electrocardiogram is of considerable clinical importance in cases of congenital and acquired heart disease. Just how reliable and specific are the currently employed electrocardiographic criteria for the diagnosis of anatomic RVH? If there is electrocardiographic RVH, can it be concluded that there is definite anatomic RVH? If the electrocardiogram does not exhibit RVH, can significant anatomic hypertrophy of the right ventricle be excluded?

The answers to these questions are best secured from electrocardiographic-pathologic correlation studies.[1]

The more commonly employed electrocardiographic criteria for RVH may be listed: right axis deviation (RAD) of +110° or more; R in Lead V_1 7 mm. or greater; R in Lead V_1 plus S in Lead V_5 (V_6) greater than 10.5 mm.; R/S ratio greater than 1 in Lead V_1 (V_{3R}, V_{4R}); R/S ratio in Lead V_5 (V_6) of 1 or less; delay in the onset of the intrinsicoid deflection in Lead V_1 (V_{3R}) 0.035 to 0.055 sec.; S-T segment depression and T-wave inversion in right precordial leads; R in Lead aV_R of 5 mm. or greater; Q/R ratio in Lead aV_R of 1 or less; qR pattern in Lead V_1 (V_{3R}); rSR′ in Lead V_1 (V_{3R}) with R′ of 10 mm. or greater (QRS duration less than 0.12 sec.).

Because of the normal right ventricular dominance in infancy and early childhood, the electrocardiographic criteria for RVH in this age group must be modified somewhat. The absolute height of the R waves and the R/S ratio in the right precordial leads, as listed above, cannot be employed. RAD must be +120° or greater to be significant in this age group. Positive T waves in the right precordial leads in infants, after the first 48 hours of life, are indicative of RVH.

The accuracy of the electrocardiographic diagnosis of RVH has ranged from 23 to 100 per cent in various autopsy-controlled series. The diagnosis of RVH is most accurate in cases of congenital heart disease (86 to 100 per cent), moderately accurate in cases of RVH secondary to mitral stenosis and cor pulmonale (75 per cent or less), but commonly undetected in cases of right heart enlargement secondary to left ventricular failure.[1] The frequently more striking evidence of electrocardiographic RVH in congenital than in acquired heart disease may be related to several factors: RVH develops at an earlier age, often when physiologic right ventricular dominance is still present; the right ventricular pressures and pulmonary vascular resistances are often greater; the degree of anatomic RVH is often more marked; left ventricular enlargement is commonly not present; there may be an actual increase in the number of myocardial fibers (hyperplasia).[1,2]

No correlation has been found by most workers between right ventricular thickness, total heart weight, left ventricular/right ventricular (LV/RV) thickness ratio, and any specific electrocardiographic pattern of RVH.[1] It has been found, however, that electrocardiographic evidence of RVH occurs more frequently as the thickness of the right ventricle increases.[3] Carouso and

associates[4] observed that the LV/RV weight ratio must be below 1.00 before electrocardiographic RVH is manifest, and that when the R/S ratio is abnormal both in Lead V_1 and Lead V_5 (V_6), anatomic RVH is extreme. Goodwin and Abdin[2] have recently reported a positive correlation between the RV/LV thickness ratio and the R/S ratio in Lead V_{4R}, as well as a trend for electrocardiographic RVH to increase with increasing RV/LV ratios.

When RVH develops, the mean spatial QRS vector increases in magnitude and is directed rightward and anteriorly. The rightward direction results in RAD, and the anteriorly directed initial force results in increased amplitude and duration of the R waves in the right precordial leads. Phillips[5] has demonstrated that RAD occurs earlier than the changes in the right precordial leads in the development of RVH in cases of cor pulmonale. He concluded that those electrocardiographic criteria which depended primarily on anteriorly directed forces detected only the more advanced RVH, whereas criteria based on rightward direction of the major electrical forces tended to detect lesser degrees of RVH, and that those patients who had both anteriorly as well as rightwardly oriented forces had the heaviest hearts with the thickest right ventricular walls.[5]

The significance of the rSR′ pattern is beyond the scope of this presentation and has been discussed elsewhere.[1] Although the pattern of incomplete right bundle branch block (IRBBB) has been considered by some as presumptive evidence of RVH, the correlation between the occurrence of the rSR′ pattern and anatomic evidence of RVH has varied.[1] Booth and associates[6] found 16 of 28 cases (60 per cent) with IRBBB to have anatomic RVH, and of 8 patients who displayed an R′ greater than 10 mm., only 5 had anatomic RVH (isolated or in combination with LVH).

Although the concept of systolic and diastolic overloading of the ventricles is of considerable interest, to our knowledge there have been no extensive careful autopsy-controlled correlations with the electrocardiographic patterns.[1,7] Such an evaluation, in fact, might be difficult because the systolic and diastolic overload concept implies a physiologic or hemodynamic rather than an anatomic alteration in the ventricles. In brief, systolic overload of the right ventricle (pulmonary stenosis, severe pulmonary hypertension) produces tall R waves in the right precordial leads; at autopsy, these cases exhibit thickening of the free wall of the right ventricle. Diastolic overload of the right ventricle (atrial septal defect, ventricular septal defect) manifests itself by IRBBB, and at autopsy, right ventricular dilatation is found.

A false-positive electrocardiographic diagnosis of RVH may result from a variety of causes. Factors which may contribute to such false-positive diagnoses include strictly posterior myocardial infarcts and the Wolff-Parkinson-White syndrome (Type A), both of which may produce abnormally tall, broad R waves in the right precordial leads. A high R wave in Lead V_1 also may be an expression of a diastolic overload of the *left* ventricle.[7] Anterolateral infarcts which produce an rS configuration in the left precordial leads may, on occasion, be confused with RVH. RAD is known to occur in some normal hearts and also in some cases of isolated left ventricular hypertrophy. Shift of the transition zone to the right in what has been termed "counterclockwise" rotation, dextrocardia, dextroposition, dextrorotation, as well as misplacement of the right precordial electrodes may, on occasion, lead to an erroneous diagnosis of RVH. Utilization of adult criteria in the younger age group also may lead to error.

Of considerable interest have been the observations of occasional cases of anatomic LVH which have exhibited electrocardiographic evidence of RVH,[8,9] and of occasional cases of isolated anatomic RVH which have displayed abnormal LAD.[3] Conditions which are known to interfere with the electrocardiographic recognition of RVH include associated LVH[2,8] and left bundle branch block. Electrocardiographic RVH may also simulate an anteroseptal infarct.

In summary, the following observations may be made: Lesser degrees of anatomic RVH are commonly undetected in the electrocardiogram, and even more marked RVH is often missed, especially in the presence of associated LVH or left ventricular conduction defects. The electrocardiographic diagnosis of RVH is most accurate in the cases of RVH of congenital heart disease (tetralogy of Fallot, pulmonic stenosis, etc.), moderately accurate in the cases of RVH of mitral stenosis and cor pulmonale, and least accurate in the cases of RVH secondary to left ventricular failure. The electrocardiographic criteria which depend on both rightward as well as anteriorly directed forces (resulting in RAD and tall R waves in right precordial leads) are more accurate and specific than those criteria which depend on only either rightward or anteriorly directed forces.

Although in most instances in which the pattern of RVH is encountered in the electrocardiogram, the diagnosis will be substantiated at autopsy, yet Walker and associates[9] found that 4 of 12 patients presenting this pattern did not have RVH at autopsy.

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Some Reflections on Zero Potential in Electrocardiography

So-called unipolar electrocardiographic leads have commanded wide clinical and theoretical interest for more than a quarter of a century. It is well recognized that there is really no such entity as an absolute unipolar lead, since devices which measure potential, including the electrocardiograph, are limited to the registration of relative, rather than absolute, potentials. Although mathematical solutions of various problems in electrical potential may give the appearance of absolute quantification, they actually contain an additional constant term which is usually suppressed because its value cannot be determined. Even if the constant term were retained in the formal solution, it would automatically disappear when attention was focused on the physical reality of differences in potential rather than on the abstraction of absolute potential.

A less puristic approach, in which the constant term is discarded because it contributes nothing to the flow of cardiogenic electrical currents throughout the body, can lead to the development of unipolar electrocardiographic lead systems which are not necessarily lacking in merit. As will be seen presently, the defects which such lead systems may contain are not related to the missing term of constant electrical potential.

As a specific example of a possible unipolar lead system, let a pithed frog be immersed in a very large volume of electrolyte which is so dilute that it does not produce significant short-circuiting of electrical potentials on the body surface. Next, let the difference in potential be recorded between two electrodes which have been introduced into the immersion fluid—one of the electrodes is placed on the body surface, and the other at a relatively remote location. Since the remote electrode is virtually insensitive to the electrical effects of the heart, it is essentially an "indifferent" electrode, and the recorded difference in potential between the two electrodes is a "unipolar" electrocardiogram.

From a somewhat different point of view, the indifferent electrode in the preceding example is so remotely located that it effectively averages the potentials on the body surface of the immersed subject. This consideration raises some hope for the eventual clinical application of the remote-

electrode technique, since it is possible, admittedly by laborious and painstaking means, to average the potentials on the body surface of human subjects. With this prospect in mind, we investigated the factors which determine the average boundary potential of homogeneous circular discs and spheres that contain either a source-sink or dipole generator of electrical current.[1]

The average boundary potentials were found to be:

	Circular Lamina	*Spherical Conductor*
Source-sink pair	$\frac{\rho I}{2\pi} \ln \frac{f_1}{f_2}$	$\frac{\rho I}{4\pi R} \ln \frac{f_1}{f_2}$
Dipole generator	$\frac{\rho M_r}{2\pi f R}$	$\frac{\rho M_r}{4\pi f R^2}$

here ρ is the specific resistivity of the conducting medium, I is the current strength of the source-sink pair, M_r is the radial component of the dipole moment, R is the radius of the conductor, f, f_1, and f_2 are the eccentricities of the dipole, source, and sink locations, respectively.

These average values are not generally zero. Nevertheless, they are identical to those potentials which would have occurred at the remote electrode had the artifice of immersion in a highly resistive medium been employed. Although it is not necessary to do so, the average (or remote) potential may arbitrarily be taken as zero by introducing the terms of potential given in the preceding table as subtractive constants superimposed on the nonconstant terms of the electrical field. The constant terms pertaining to the circular lamina are identical to those which Nelson[2] obtained by taking a remote electrode located in a highly resistive immersion medium as the "zero of potential."

At this juncture one may ask whether the type of electrode application which averages boundary potentials actually results in unipolar electrocardiographic leads. Some penetrating answers are obtained by examining the type of lead field which is produced by causing one unit of electrical current to flow from a single electrode on the body surface to an averaging network composed of numerous, properly weighted and located electrodes.

In the case of the homogeneous circular disc, the form of the lead field thus produced is virtually identical to that obtained by causing electrical current to flow from an interior point to the periphery of an extended, plane conducting sheet. Thus, averaging the boundary potentials of a circular lamina is an artifice which satisfies quite nicely McFee and Johnston's[3] criterion of a unipolar electrocardiographic connection. The only effect of the circular boundary is to double the sensitivity of the connection.

In the case of the spherical conductor, it has been shown that the form of the lead field between a single surface electrode and multiple averaging electrodes differs significantly from that generated by a current unipole located in an extended, homogeneous, conducting medium.[4] Therefore, the lead connection fails to satisfy McFee and Johnston's criterion of unipolarity. However, the connection does possess a kind of electrocardiographic "indifference," characterized by the fact that only the orientation, and not the form, of the lead field is affected by altering the location of the surface of the single electrode.

The design and analysis of systems of averaging electrodes is more complicated in the case of elliptical laminas and ellipsoidal volume conductors. For instance, the weighting factor per small unit of boundary is constant in the case of the circular lamina or sphere. This simple relationship does not apply to the ellipse and the ellipsoid. Furthermore, the employment of an averaging electrode does not result in a boundary-free type of unipolar lead field in either of these two cases. Finally, the form, as well as the orientation, of the lead field is affected by altering the location of the exploring surface electrode.

The electrocardiographic literature contains descriptions of averaging electrodes that consist of belts containing one or more rows of resistor-weighted electrodes, and which are applied to the surface of the torso at approximately the mid-ventricular level.[5] We investigated the validity of such an array of electrodes in the case of a spherical volume conductor containing a current dipole which was located eccentrically in the plane of the equator.[1] We found that the average

potential on the surface of the sphere differed significantly from the average potential around its equator, and that the disparity between the two values increased as the eccentricity of the dipole location was increased. It was also apparent that the quality of electrocardiographic indifference, described previously in the case of the surface-averaging electrode, was lost when the averaging electrode at the equator was substituted. This is not to say that the grid-belt type of electrode may not have special merit in clinical application (as, indeed, it may), but recommendation of the device as a strict zero-of-potential reference does not appear to be warranted.

Much the same conclusions can be drawn in the case of an indifferent electrocardiographic terminal which is composed of two or three resistor-weighted electrodes. The validity of such relatively simple arrays can be interpreted on the basis of whether or not the concept of the single, fixed-location, equivalent cardiac dipole provides a sufficiently accurate first approximation of electrocardiographic behavior. We have attempted to approach the problem in this way, but have generally found it more rewarding once again to invoke the concept of the lead field.

Implicit in the McFee-Johnston principles is a method for applying a different type of unipolar electrocardiographic connection to homogeneous volume conductors of various shapes. This method is similar to the remote-electrode equivalent technique to the extent that an electrocardiographic terminal composed of numerous resistor-weighted electrodes applied to the surface of the conductor is required. In contrast to the other technique, the purpose of the electrode-resistor array is not to reproduce the potential of a remote electrode (except fortuitously in the case of a homogeneous circular disc), but rather to form a connection which obeys precisely the solid-angle law of heart-lead relationships. To state the properties of the McFee-Johnston unipolar connection somewhat differently, its lead field is identical in form to that of a unipolar electrode immersed in an infinite, homogeneous conducting medium. The desirable property of electrocardiographic augmentation due to boundary effects is retained in this type of unipolar connection, but it tends to be less than the augmentation factors of conventional bipolar leads.

Rather paradoxically, then, there appear to be two theoretically correct methods for recording unipolar electrocardiograms. One method is in accordance with the physicist's definition that electrical potential is directly proportional to the amount of energy expended in moving a unit positive charge from infinity to the point at which the potential is being determined. The other method of unipolar registration is one which satisfies the solid-angle law of electrocardiography. Assuming that it be equally practical to construct either lead system, we would favor the latter because its electrocardiographic properties are known by definition. The corresponding properties of the other lead system are not so well known, and require clarification.

Devising any significant number of leads of the solid-angle type poses a monumental task. On the other hand, if the human body were idealized into an ellipsoid, it is likely that an approximation of the remote-equivalent lead terminal could be applied for investigative purposes without an unreasonable amount of labor. Immersion techniques have been repeatedly advocated and tested as a means of achieving a remote-equivalent electrocardiographic connection. As suggested by the hypothetical experiment described earlier, we feel that the method could be made to function correctly when applied to electrocardiography in the frog, but we are less certain of application to human beings. Apart from a consideration of the rather formidable technical aspects which are involved, clear evidence should be sought that the passive electrical properties of the human integument do not invalidate the underlying principles of the method.

Intriguing though theoretically ideal unipolar electrocardiography may be, the prospects for practical clinical implementation appear dim.

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Mechanisms of Lipid Accumulation in Atherogenesis

The mechanisms concerned in the accumulation of lipids in an atheromatous plaque are as yet far from clear. The intima of the larger arteries, in which the lipids are initially observed, consists of a single layer of flattened endothelium beneath which is a mucinous ground substance containing a fibroelastic network. This tissue is avascular and does not contain lymphatics. If the filtration theory of atherogenesis is valid, the lipids, in the form of large lipoprotein molecules or particles, must penetrate the arterial endothelium.

This hypothesis has led to further studies of the fine structure of the aortic endothelium, aided by the use of the electron microscope.[1] The structure of the endothelial cells of the large arteries corresponds closely to that described by several investigators[2,3] for capillary endothelium. Both contain numerous small vesicles or invaginations of the plasma membrane, but no fenestrations or pores have been observed either in the so-called intercellular cement or in the cells themselves. The exact nature of the "cement" lines of the endothelium has been investigated,[4] but no anatomic structure could be found corresponding to what has been usually termed "the intercellular cement," although the space between adjacent cells must contain some substance.

Colloidal particles of thorium dioxide, injected intravenously, passed into the cytoplasm of the endothelial cells and were observed to be confined to the membrane-bounded vesicles, but no particles entered the intercellular boundaries.

These findings suggest that lipoproteins and lipid particles might also enter the endothelial cells through these small vesicles rather than through fenestrations or pores in the intercellular cement. In an endeavor to clarify the mechanisms concerned in the transport of lipid across the vascular endothelium, the aortic endothelium of hypercholesterolemic rabbits has been investigated.[5] Some of the endothelial cells, those overlying atheromatous plaques, contained droplets of lipid in their cytoplasm, whereas those cells not over plaques usually contained little or no demonstrable lipid. This may mean that the large lipid molecules or particles pass into and, probably, through some endothelial cells in patches scattered throughout the aorta, but not through all cells. These observers also found lipid-laden macrophages on both sides of the endothelium and actually passing between the endothelial cells over a plaque. The origin of these macrophages is still subject to controversy, but one view would be that the lipids having passed through the endothelial cells are engulfed in the subendothelial tissue by macrophages which may then pass through the endothelium.

That the large lipoprotein complexes present in the plasma of hypercholesterolemic rabbits can pass through capillary endothelium, similar in structure to aortic endothelium, has been shown by collecting lymph from the paws of these animals.[6] All the lipoproteins observed in the plasma are present in the lymph, but in much lower concentrations, and the lymph is often opalescent because of the presence of lipids in particulate form. If the skin capillaries are injured, the lipids in the lymph, and, therefore, in the tissue fluid, greatly increase in concentration, and the lymph becomes milky if the plasma is milky.[7,8] Although this rapid passage of particulate lipids through the endothelium of the skin capillaries occurs in hypercholesterolemic rabbits, the lipid particles of an artificial fat emulsion or of thoracic duct chyle injected into the blood stream do not readily penetrate the endothelium. It seems probable that the size of the lipid particle is important in this respect; the particles in hypercholesterolemia are smaller than those of chyle or the artificial fat emulsion used.

These experiments on the permeability of skin capillaries to lipids may throw some light on the passage of lipids through the aortic endothelium. It may be that whereas chylomicrons of chyle, consisting mainly of triglyceride, do not penetrate the vascular endothelium of the large

arteries, even when injured, the smaller cholesterol-rich lipoproteins will. We have no direct information, however, concerning the extent of this filtration in normal or hypercholesterolemic individuals. The accumulation of lipid in atheroma may be due to an increase in the normal amount of filtration; or it may be only in certain abnormal conditions of injury that lipoproteins pass through the aortic endothelium to accumulate in the intima. This may to some extent account for the patchiness observed in the distribution of atheromatous plaques.

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The Acid Mucopolysaccharides

In the animal body is found a group of substances which have attracted interest from basic scientists and clinicians because of peculiar chemical structure and biologic activity. They are outstanding in the content of acidic radicles (sulfate, carboxyl) attached to a polysaccharide moiety. Examples are the chondroitin sulfates, the heparins, heparitins, hyaluronic acid, and acid mucins.[1]

Alpha-heparin has been under active study since its discovery 44 years ago. It has been implicated in several unrelated processes, a few of which are: anticoagulant activity,[2] lipid metabolism,[3] and perhaps vasodilation.[4]

The role of acid mucopolysaccharides in lipid metabolism is a topic of current interest because of a hypothetical relationship between arterial changes and lipids. After injection of heparin a lipid clearing factor appears in blood.[5,6] This has the property of a lipoprotein lipase, and as a consequence the concentration of nonesterified fatty acids (NEFA) in plasma increases.[7] It is very likely that fatty acids enter metabolic processes common to fat and carbohydrate. Since fatty acids are a ready source of energy for muscle metabolism, the level of NEFA in plasma may markedly influence the efficiency of muscular work.[8]

However, changes of NEFA in blood can be induced by several agents other than heparin. Whereas feeding of fat or glucose or injection of insulin causes a fall in the concentration of NEFA in plasma, adrenaline causes a marked rise.[9]

Furthermore, lipid metabolism is influenced by a lipid mobilizing hormone of the posterior pituitary gland, and lipid mobilization is inhibited by the oral administration of a partially depolymerized hyaluronic acid.[10]

It is perhaps significant in this connection to point out that acid mucopolysaccharides are present in aortic tissue[11,12] and that heparin-like activity is stated to be higher in blood vessels of children than in those of adults.[13]

It is certain, however, that heparin is not specific in its actions. The structural requirements for anticoagulant and lipemia clearing activities are not the same. Whereas both nitrogen and

oxygen sulfonated radicles are essential for anticoagulant activity, the clearing effect can be obtained with compounds in which the sulfate groups are replaced by other acid radicles.[14] The advantage of materials devoid of anticoagulant activity but with potent clearing activity is obvious.

Despite the fact that α-heparin is present within certain cells, its occurrence in normal circulating blood is not established. There is great discrepancy between the results obtained by unrelated techniques. Whereas determinations depending on the thrombin clotting time indicate that normal blood contains, at most, traces of heparin, determinations based on metachromatic staining give considerably higher results. The latter techniques, however, are not specific for heparin, and it has not been shown that this material has anticoagulant properties.[15] It is possible that heparin or a derivative of it is a component of the clearing factor isolated from plasma.[16]

It is well established that heparin has no effect either as anticoagulant or as activator of the clearing factor when given by mouth, but exerts its effect only after injection. However, several reports have appeared which indicate that mucins isolated from the gastrointestinal tract can be taken orally and have an effect on lipid metabolism.[17,18]

From this brief review it is apparent that a number of facts have been established, but a number of uncertainties concerning the biologic activities of the acid mucopolysaccarides remain and further work is required to define more clearly their role in biologic processes.

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Letter to the Editor

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JUNE 9, 1960

To the Editor:

As a subscriber to the *American Heart Journal*, I read the Clinical-Pathologic Conference in the May, 1960, issue concerning an infant with an "atypical origin of the right pulmonary artery."

The authors discuss the possibility of making the correct diagnosis preoperatively but have no experience of their own. They express the opinion that "no one knows the future of a child with only one functioning pulmonary artery."

We have just observed two similar cases at the Universitäts-Kinderklinik, Kiel, Germany; one infant had an absent right pulmonary artery, and the other, an 8-year-old boy, had an additional patent ductus arteriosus. In both cases the diagnosis could be made preoperatively.

In reviewing the literature,[1] we found some thirty cases in which there was an absent right pulmonary artery. In this group "with only one functioning pulmonary artery" the chance of life has been good. The oldest living patient is 58 years old. In one third of the patients this anomaly is accompanied by a patent ductus arteriosus. There are some patients with this combination who are still living; some died in the third decade of life.

Finally, descriptions exist of a 23-year-old man[2] with just the same anomaly described in the paper from the Mayo Clinic, and of a woman with absent right pulmonary artery, in whom a vessel from the ascending aorta supplied the right lung, but who had an aortic septal defect instead of a patent ductus arteriosus.[3] This woman reached an age of 25 years before she died in cardiac failure.

I think that these cases shed some light on the prognosis of children with "only one functioning pulmonary artery," and for this reason this letter may be of interest to readers of the Journal.

By the way, there is obviously a misprint in the *Diagnosis* of the afore-mentioned Clinical-Pathologic Conference, because the atypical right pulmonary artery originates from the *ascending* and not the descending aorta.

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Book Review and Announcement

BASIC FACTS OF BODY WATER AND IONS. By Stewart M. Brooks, M.S., Science Instructor, Lasell Junior College, Auburndale, Mass.; Instructor in Pharmacology, Boston City Hospital School of Nursing, and Children's Hospital School of Nursing, Boston, Mass. New York, 1960, Springer Publishing Co., Inc., 159 pages, 18 illustrations. Price $2.75.

Mr. Brooks directs his book to "the student and practitioner of nursing, medical technology, and pharmacy," and, as a refresher, "to the student and practitioner of medicine."

The book is divided into two parts. Part I, "The Facts Explained" is quite interestingly written. However, the material is explained in too great detail for any but beginning students, who, it is expected, will not have use for a book on this subject.

Part II, "The Facts Applied" is written in a different manner, and is primarily a lengthy list of the cases in which fluid and electrolyte therapy is used, with some discussion of the solutions used in each case and the purposes of their use. This portion of the book would be good for reference, but for students of these subjects it should be more fully explained and related to the information given in the first part of the book.

The book also contains a glossary, which would be good for emphasis in teaching. The illustrations are excellent.

THE AMERICAN COLLEGE OF CARDIOLOGY will hold its NINTH INTERIM MEETING concurrently with the 33RD ANNUAL MEETING OF THE AMERICAN HEART ASSOCIATION at Kiel Auditorium in St. Louis, Mo., Oct. 21-23, 1960, according to an announcement by Gabriel F. Greco, M.D., Chairman, Publicity Committee, Ozone Park, N. Y. The American College of Cardiology jointly with the American Heart Association will feature a presentation of the latest methods in diagnosis: ear oximetry, objective evidence of cardiac impairment, functional tests, mechanisms and biochemical tests. There will be a symposium on atrial arrhythmias. The College will also present jointly with the A.H.A. its annual popular Fireside Conferences, designed to gather around specialists and investigators in basic and clinical research all cardiologists interested in the exploration and development of new fundamental, diagnostic, therapeutic measures in the fight against heart disease. There will be panel discussions on techniques of major vessel replacement, cardiac function tests, evaluation of radiographic techniques for measuring cardiac output, cardiac resuscitation, the effect of environment and stress, changes in myocardial metabolism, management of cor pulmonale, refractory cardiac failure, rheumatic heart disease, hyperlipemia, congestive failure, cardiogenic shock, fibrinolysis, hypertension, and surgery for insufficient and for stenotic valves.

Among the prominent participants will be Louis F. Bishop, New York, President of the American College of Cardiology, and A. Carlton Ernstene, Cleveland, President of the American Heart Association, Michael DeBakey, Houston, Tex., C. H. Hufnagel, Washington, D. C., Charles F. Bailey, New York, William Dock, New York, George C. Griffith, Los Angeles, Robert A. Grant, Bethesda, George E. Burch, New Orleans, Myron Prinzmetal, Los Angeles, Richard J. Bing, Detroit, Meyer S. Friedman, San Francisco, E. Grey Dimond, Kansas City, Kans., and John S. LaDue, New York, dynamic chairman of the Program Committee of the American College of Cardiology. Dr. Louis F. Bishop will preside at the sessions of the College and the joint program, and conduct on Friday evening, October 21, the Fireside Conferences which the American College of Cardiology will jointly present with the American Heart Association's Council on Clinical Cardiology.

Full information of interest to those planning to attend the program may be obtained from Dr. Philip Reichert, Executive Director, American College of Cardiology, Empire State Building, 350 Fifth Avenue, New York 1, N. Y.